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VOLUME 80 NUMBER 3

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SEPTEMBER 1947

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second Class Matter Jan. 25, 1909, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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ARCHIVES of INTERNAL MEDICINE

VOLUME 80 SEPTEMBER 1947 NUMBER 3

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SARCOIDOSIS

A Clinical and Roentgenologic Study of Twenty-Eight Proved Cases

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WHILE serving in an army general hospital which functioned as a center for radiation therapy, we were afforded an opportunity to study a large number of mediastinal tumors. A clinical and histologic diagnosis of sarcoidosis was established in 28 cases. It was thought worth while to assemble this group of cases and assess the values of the clinical and roentgenologic features of the disease. The most pressing problem in the diagnosis of a mediastinal tumor is the differentiation of benign from malignant lymphogranuloma. The factors bearing on this differential diagnosis are presented.

Since Besnier [1] described lupus pernio in 1889 and Boeck [2] ten years later studied the histologic structure in his cases of "multiple benign sarcoid of the skin," dermatologists have become increasingly aware of the cutaneous features of the disease. It was not until Schaumann [3] in 1914 first realized that the cutaneous lesions described by Besnier and Boeck were in reality only a part of a generalized disease with characteristic pathologic changes in various internal organs that the present sound concept of the disease was possible. Jüngling's [4]

1. Besnier, E.: Lupus pernio de la face; synovites fongeuses (scrofulotuberculeuses); symétriques des extrémités, Ann. de dermat. et syph. **10**:333-336, 1889.

2. Boeck, C.: Multiple Benign Sarcoid of the Skin, J. Cutan. & Genito-Urin. Dis. **17**:543-555, 1899.

3. Schaumann, J.: Lymphogranulomatosis Benigna in the Light of Prolonged Clinical Observations and Autopsy Findings, Brit. J. Dermat. **48**:399-410, 1936.

4. Jüngling, O.: Ueber Ostitis tuberculosa multiplex cystoides, zugleich ein Beitrag sur Lehre von den Tuberkuliden des Knochens, Beitr. z. klin. Chir. **143**:401-475, 1928.

description of the characteristic bony changes on roentgen study and Heerfordt's [5] description of uveoparotid fever are notable contributions.

PATHOLOGIC ANATOMY

Little is known of the pathogenesis of the disease. Schaumann [3] in 1924 discussed the relationship to tuberculosis and the different states of immunity present in the two diseases as indicated by the sensitivity of the skin to tuberculin. In 1936 he raised the question of a pleomorphic variant of the tubercle bacillus as the cause of sarcoid. This work has not been substantiated by other investigators.

Tubercle bacilli have been found by several workers in sarcoid lesions; however, the question always remains as to whether or not the patient had the two diseases concomitantly. The presence of tubercle bacilli in lesions of sarcoid has been reported by Rubin and Pinner,[6] Hollister and Harrell,[7] Reisner [8] and Dorgeloh and Tully.[9] Goeckerman [10] once thought that tubercle bacilli could be found only in the early lesions. In a number of cases which have been followed over a period of years, frank tuberculosis has been seen to develop in conditions clinically and histologically diagnosed as sarcoid. The development of tuberculosis is one of the frequent causes of death in sarcoid, and the relationship is thought to be more than coincidental by most writers (Pinner,[11] Rubin and Pinner [6], Reisner,[8] Schaumann [3] and Harrell [12]). However, it must be admitted that definite proof of the tuberculous nature of sarcoid is still lacking.

In 1914 Schaumann [3] described involvement of the tonsils in nearly all the patients examined by him. Enlargement of the tonsils was noted in only 2 of our patients. One of these had his tonsils removed elsewhere, while the other had them removed at our hospital and the lesions

5. Heerfordt, C. F.: Ueber eine "Febris uveo-parotidea subchronica" an der Glandula Parotis und der Uvea des Augus lokalisiert und häufig mit Paresen cerebrospinaler Nerven kompliziert, Arch. f. ophth. **70**:254-273, 1909.

6. Rubin, E. H., and Pinner, M.: Sarcoidosis: Case Report and Literature Review of Autopsied Cases, Am. Rev. Tuberc. **49**:146-169, 1944.

7. Hollister, W. F., and Harrell, G. T.: Generalized Sarcoidosis of Boeck Accompanied with Tuberculosis and Streptococcic Bacteremia, Arch. Path. **31**:178-181 (Feb.) 1941.

8. Reisner, D.: Boeck's Sarcoid and Systemic Sarcoidosis: A Study of Thirty-Five Cases, Am. Rev. Tuberc. **49**:289-307 and 437-461, 1944.

9. Dorgeloh, R., and Tully, P. W.: Relationship of Boeck's Sarcoid and Tuberculosis, Arch. Path. **40**:309-311 (Nov.-Dec.) 1945.

10. Goeckerman, W. H.: Sarcoid and Related Lesions, Arch. Dermat. & Syph. **18**:237-262 (Aug.) 1928.

11. Pinner, M.: Non-Caseating Tuberculosis, Am. Rev. Tuberc. **37**:690-720, 1938.

12. Harrell, G. T.: Generalized Sarcoidosis of Boeck, Arch. Int. Med. **65**:1003-1034 (May) 1940.

of sarcoid were found therein (case 27). There are few reports of sarcoid in the tonsils in the American literature. The failure to observe tonsillar involvement in this country as compared with the Scandinavian countries may be the result of the much more frequent performance of tonsillectomy in childhood here.

Cerebral manifestations of sarcoid have been known to occur. Roos [13] collected 8 cases of "lymphogranulomatosis benigna" in which there were neurologic signs. In 3 fatal cases which were studied histologically there were basal lesions; in 2 these were located in the brain and in the other in the meninges. Most of the other patients showed signs indicating a basal location of the lesion, and 2 had diabetes insipidus. Kraus [14] reported the autopsy observations in an instance of sarcoidosis with clinical diabetes insipidus.

In 6 autopsies Nickerson [15] found sarcoid lesions in the spleen in 6 instances and in the lungs in 4. Unusual localizations were found in the myocardium, endocardium, pancreas, testis and vertebral and femoral bone marrow. Chronic interstitial myocarditis was found in 2 of 4 cases studied pathologically by Schaumann,[3] while Longcope and Fisher [16] found sarcoidosis in both the myocardium and the pericardium in 2 patients. There was strong presumptive evidence of pericardial involvement in case 10 reported in this paper. Involvement of the kidney has been suspected in the sarcoid process during life (Nordin,[17] Schaumann,[3] and Rotenberg and Guggenheim [18]), but it has been found infrequently at autopsy (Spencer and Warren [19]). Two instances of isolated sarcoidosis of the small intestine, simulating nonspecific ileojejunitis, have been reported with the findings at operation (Watson, Rigler, Wagensteen and McCarthy [20]). One of Longcope's patients had sarcoid disease of the testicles and epididymis, with a eunuchoid state.

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13. Roos, B.: Cerebral Manifestation of Lymphogranulomatosis Benigna (Schaumann) and Uveoparotid Fever (Heerfordt), Acta med. Scandinav. **54**:123-130, 1940.

14. Kraus, E. J.: Sarcoidosis (Boeck-Besnier-Schaumann Disease) as Cause of a Pituitary Syndrome, J. Lab. & Clin. Med. **28**:140-144, 1942.

15. Nickerson, D. A.: Boeck's Sarcoid: Report of Six Cases in Which Autopsies Were Made, Arch. Path. **24**:19-29 (July) 1937.

16. Longcope, W. T., and Fisher, A. M.: Involvement of the Heart in Sarcoid, J. Mt. Sinai Hosp. **8**:784-797, 1942.

17. Nordin, G.: Maladie de Schaumann (lymphogranulomatose benigne) avec plaques erythrodermiques et iridocylite comme symptomes cliniques dominants, Acta med. Scandinav. **104**:131-136, 1940.

18. Rotenberg, L., and Guggenheim, A.: Boeck's Sarcoid: Report of Case with Renal Involvement, Dis. of Chest **8**:392-395, 1942.

19. Spencer, J., and Warren, S.: Boeck's Sarcoid, Arch. Int. Med. **62**:285-296 (Aug.) 1938.

20. Watson, C. J.; Rigler, L. G.; Wagensteen, O. H., and McCarthy, J. D.: Isolated Sarcoidosis of the Small Intestine Simulating Non-Specific Ileojejunitis, Gastroenterology **4**:30-50, 1945.

In all the cases presented in this paper the diagnosis was made by histologic examination and confirmed by the Army Medical Museum. Since enlargement of the peripheral lymph nodes is common in this disease, an accessible lymph node can easily be removed. In our experience the cervical region has been the optimum site for removal of material for biopsy; however, the surgeon should not hesitate to remove small, innocent-appearing nodes, as these will frequently show the typical lesion. It is best to avoid the inguinal region in seeking material for biopsy, as the nodes in this region almost always show varying degrees of nonspecific inflammation and a definite diagnosis is difficult to establish. In addition to the peripheral lymph nodes, we have secured satisfactory material from the following structures: tonsils, parotid glands, lacrimal glands, skin and mediastinum. Aspiration of biopsy material from the liver was performed successfully in 11 of 14 cases by van Buchem.[21] He recommended it when other sources were not available.

Microscopically there is proliferation of the epithelioid cells, with the formation of granulomas. Giant cells of the Langhans type are present. The rare occurrence of peculiar basophilic cytoplasmic inclusions in giant cells has been described (Moore[22]). In the lymph nodes the granulomas are arranged in clusters which may fill the entire node, but they usually do not break through the capsule. Lesions have been found to undergo fibrosis and replacement with hyalinized connective tissue (Bruce and Wassen[23]), and the presence of a large amount of collagen is taken to indicate a healing or healed process (Nickerson[15]), although King[24] questioned the statement that the sarcoids are replaced by fibrous tissue. The center of these tubercles may show slight necrosis, but true caseation is rare.

In a study of the bone marrow of 3 patients, Lucia and Aggeler[25] found a picture simulating a chronic infectious process. There was no evidence of depression of hemopoiesis in the marrow. A normal marrow was found in the single case studied by us. In the liver it has been noted that the lesions of sarcoid are more numerous in the portal triads,

21. van Buchem, F. S. P.: On Morbid Conditions of the Liver and the Diagnosis of the Disease of Besnier-Boeck-Schaumann, Acta med. Scandinav. **123**:151-153, 1946.

22. Moore, R. A.: A Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1944, pp. 544-545.

23. Bruce, T., and Wassen, E.: Clinical Observations on Course and Prognosis of Lymphogranulomatosis Benigna (Schaumann), Particularly in Regard to Pulmonary Lesions, Acta med. Scandinav. **104**:329-343, 1940.

24. King, D. S.: Sarcoid Disease as Revealed in the Chest Roentgenogram, Am. J. Roentgenol. **45**:505-512, 1941.

25. Lucia, S. P., and Aggeler, P. M.: Sarcoidosis (Boeck): Lymphogranulomatosis Benigna (Schaumann) Observations on the Bone Marrow Obtained by Sternal Puncture, Acta med. Scandinav. **104**:351-365, 1940.

with only a few in the midzones of the lobules. In miliary tuberculosis the reverse is said to be true (Nickerson [15]). Endarteritis of the pulmonary vessels which resulted in failure of the right side of the heart was found in a patient at autopsy by Tice and Sweany.[26] In their patient the lesions of the pulmonary parenchyma were healed or healing when death occurred.

CLINICAL OBSERVATIONS

The manifestations of this disease are many and varied because of the number of organs and tissues which may be involved (Schaumann [3] and Klemperer [27]). In general, it may be said that about four clinical types are recognized as they present themselves to the physician. These are: (1) the sarcoids of the skin as described by Boeck and Besnier; (2) the uveoparotid fever of Heerfordt; (3) the type with lymphadenopathy of superficial or intrathoracic nodes simulating lymphoblastomas, and (4) a type in which there is primarily involvement of the pulmonary parenchyma on roentgen study and which, when there is also cough, loss of weight and slight fever, may closely resemble pulmonary tuberculosis.

The patients whose cases are presented here were admitted to an army general hospital between July 1, 1942 and April 1, 1946 (table 1). These patients were drawn primarily from young male military personnel. The hospital has functioned as a center for the treatment of tumors, and the majority of the patients sent there have symptoms simulating those of a malignant tumor. Indeed, all our patients had intrathoracic lymphadenopathy, and all except 2 had enlargement of the superficial lymph nodes. The result of this selection will immediately be seen when it is noted that 27 of the 28 patients were men, while the sex incidence in most of the previously reported series was about equal. Of the 35 cases reported by Reisner,[8] only 7 patients were males and 24 were females. In Longcope's [28] 31 patients, the ratio of males to females was 18 to 13. In the present series the age incidence was undoubtedly influenced by the aforementioned factors. Twenty-two were in the third decade of life, 6 in the fourth, only 2 in the second and 1 in the sixth. Our youngest patient was a girl 13 years of age and our oldest a man of 58. Rubin and Pinner [6] have reported an autopsy by Stein on a women of 68 years. This represents an extreme range. The majority of the patients have been in the young adult group. It is

26. Tice, F., and Sweany, M. C.: Fatal Case of Sarcoid with Autopsy Findings, Ann. Int. Med. **15**:597-609, 1941.

27. Klemperer, P., in Proceedings of the Tumor Seminar of the American Society of Clinical Pathologists, Philadelphia, June 7, 1942.

28. Longcope, W. T.: Sarcoidosis or Besnier-Boeck-Schaumann Disease, J. A. M. A. **117**:1321-1330 (Oct. 18) 1941.

TABLE 1.—*Clinical Observations*

Case	Age (Yr.), Sex, Race	Complaints	Superficial Nodes	Eyes	Comments
1	26 M N	Dyspnea and cough	None	Normal	Electrocardiogram showed right axis deviation; cor pulmonale seen at autopsy
2	20 M W	Night sweats, loss of weight and cough	Axillary and inguinal	Lacrimitis	Biopsy showed normal bone marrow; biopsy of a lymph node suggests sarcoid
3	13 F W	Fever, loss of weight (25 pounds) and anemia	Generalized	Uveitis and keratitis	Enlarged spleen; parotitis; nephritis; necrosis with caseation on biopsy
4	22 M W	Pain in the eyes and blurred vision	Axillary and inguinal	Iridocyclitis	No response to roentgen therapy with 1,350 r
5	31 M N	Cough and weakness	Axillary	Normal	Chronic tonsillitis
6	21 M N	Pain in the chest, cough and loss of weight (25 pounds)	Generalized	Normal	Normal electrocardiogram; bronchoscopy noncontributory
7	26 M N	Pain in the chest, fever, cough and dyspnea	Cervical (slight)	Iridocyclitis	Fever throughout course; nodules on the skin of legs and forearms
8	23 M N	Dyspnea and cough	Generalized	Normal	Normal electrocardiogram
9	21 M W	Chronic cough	Supraclavicular	Conjunctivitis	Amputee; tubercles with necrosis on biopsy
10	31 M W	Dyspnea, cough and pain in the chest	Generalized	Normal	No response to roentgen therapy with 1,300 r.; deviation of the right axis in the electrocardiogram; pericarditis, with effusion
11	21 M W	Pain in the chest, chest, cough and dyspnea	Generalized	Normal	Endamoeba histolytica present; deviation of the left axis in the electrocardiogram
12	18 M W	None	Cervical	Normal	.....
13	21 M W	Loss of weight (50 pounds), nausea and vomiting	Generalized	Uveitis	.....
14	25 M N	Loss of weight, headaches and edema	Generalized	Normal	.....
15	25 M W	None	Supraclavicular	Normal Normal	Spleen palpable
16	27 M W	None	Epitrochlear	Normal	.....
17	58 M W	Weakness, anemia and dyspnea	None	Negative	Splenectomy in 1945 for hemolytic anemia
18	25 M N	Dyspnea	Postauricular	Iridocyclitis; lacrimitis	Positive reaction to Kahn test for syphilis
19	19 M N	Dyspnea	Generalized	Lacrimitis; uveitis	Normal electrocardiogram
20	34 M N	None	Inguinal	Lacrimitis	Skin of the eyelids involved

TABLE 1.—*Clinical Observations—Continued*

Case	Age (Yr.), Sex, Race	Complaints	Superficial Nodes	Eyes	Comments
21	22 M N	Parotid swelling and fever	Femoral	Uveitis; lacrimitis	.....
22	23 M W	None	Axillary	Negative	Gunshot wound in the thigh
23	29 M W	Dyspnea, cough and hemoptysis	Generalized	Negative	Endamoeba histolytica present
24	20 M N	Chronic cough and dyspnea	Generalized	Negative	.....
25	38 M N	Loss of weight (50 pounds), pain in the chest and cough	Generalized	Negative	.....
26	24 M N	None	Cervical and inguinal	Negative	.....
27	24 M N	Dyspnea and fatigability	Generalized	Negative	Biopsy of material from the tonsil showed the presence of sarcoidosis; deviation of the right axis in the electrocardiogram
28	22 M N	Parotid swelling	Generalized	Uveitis	Tall P waves in the electrocardiogram; the parotid gland was shown to be infected on biopsy

significant, however, that 15 of our 28 patients were Negroes. This was much higher than the over-all ratio of Negro to white patients admitted to the hospital and is in accord with the experience of others (Longcope,[28] Harrell,[12] Thomas [29] and Pinner [11]). In European countries the disease is said to be frequent among the Scandinavian people (Hannesson [30]).

The symptoms which these patients present are variable in degree and tend to be mild. Nine of them complained of cough which was persistent and productive of only a small amount of sputum. Only 2 patients had slight hemoptysis. Eleven complained of dyspnea which was aggravated by exertion, particularly long marches or field exercises, while only 6 had mild pain in the chest. Six of them had lost a significant amount of weight, the greatest reported being 50 pounds (23 Kg.). Weakness, fever, anorexia, nausea and vomiting were occasional symptoms. Three patients had symptoms referable to the eyes only. It is noteworthy that 6 persons had no symptoms whatsoever, their disease having been discovered only by routine roentgenologic study of the chest. It was observed that cough and dyspnea were the most frequent presenting symptoms. This was probably due to the fact

29. Thomas, C. C.: Sarcoidosis, Arch. Dermat. & Syph. **47**:58-73 (Jan.) 1943.
30. Hannesson, H.: Besnier-Boeck's Disease; Review, Brit. J. Tuberc. **35**:88-113, 1941.

that all patients had intrathoracic disease. The peripheral lymph nodes were found to be enlarged in 26 of the 28 patients. The palpable nodes were small and discrete and did not tend to be confluent; in fact, the involvement of the lymph nodes was so slight in some patients as to seem clinically insignificant, so that the surgeon was often reluctant to perform a biopsy until urged to do so by the medical service. Not infrequently one of these "insignificant nodes" showed the characteristics of the disease. Reisner [8] has reported superficial lymphadenopathy in nearly 100 per cent of his series. This was also a constant finding in the series reported by Longcope [28] in 1941.

Involvement of the eye was observed in 11 of our patients. The lesion was most often a uveitis or iridocyclitis, but any or all of the structures of the eye may be involved (Levitt [31]). The ocular manifestations were as follows: uveitis in 7 cases, lacrimitis in 3, keratitis in 1 and conjunctivitis in 1. Only 3 patients had the characteristic combination of ocular disease and swelling of the parotid gland as described by Heerfordt [5] in the so-called uveoparotid fever. Moderate enlargement of the spleen occurred only three times. Reisner [8] expressed the belief that the enlargement of the spleen occurs early in the disease and then tends to undergo regression. In only 2 instances were we able to find a cutaneous lesion. In 1 of these (case 8) there was a small nodule on the forehead, which the patient stated had been present for ten years; when removed, this showed definite changes typical of sarcoid. The other patient had enlarged mediastinal lymph nodes and fever. No definite diagnosis could be made because there were no palpable lymph nodes or any obvious source for pathologic study. Repeated careful palpation of the cutaneous surface finally revealed nodules on the legs and forearms, two of which were removed and showed the characteristic structure of the disease (case 7). This low incidence of cutaneous lesions is undoubtedly due to the factors operating in the selection of these patients as described previously. A significant degree of fever, not accounted for by intercurrent infections or other disease, was present in 8 instances. The fever was usually of low grade and continued over a period of several days or weeks. Only 1 patient had hyperpyrexia over a period of three months (case 7).

LABORATORY OBSERVATIONS

Perhaps the most consistent of all the laboratory observations in this disease is the reaction to the tuberculin skin test, which in a great majority of instances is negative. This test was done in 25 of our cases, and the reaction was negative in 21, doubtful in 2 and weakly positive (2 plus) in another 2 (table 2). This anergy to tuberculin has been

31. Levitt, J. M.: Boeck's Sarcoid with Ocular Localization, Arch. Ophth. **26**:358-389 (Sept.) 1941.

TABLE 2.—*Laboratory Observations*

Case	Tuberculin Test, Reaction	Red Blood Cell Count*	Hemoglobin Content*	White Blood Cell Count*	Differential Count: Eosinophils	Differential Count: Monocytes	Calcium, Mg.	Phosphatase	Alkaline Phosphatase
1	Negative (0.1 mg.).....	3.8	70%	4.6	0	0	10.5	2.8	1.4
		5.2	100%	13.6	..	..	11.5	3.0	5.6
2	Negative.....	4.3	82%	4.4	2	3	....	...	...
3	Negative (patch test).....	4.0	73%	3.7	2	0	11	3.5	6.1
		4.7	85%	7.8	7	12	....	5.3	6.7
4	.....	4.9	90%	3.0	0	0	....	...	...
		5.4	110%	7.3	4	8	....	...	...
5	.....	...	....	4.4	..	..	....	...	...
6	Positive (0.00002 mg.).....	4.3	84%	5.6	1	0	10	3.3	5.4
		5.1	94%	9.1	13	10	11.5	3.6	7
7	Negative (patch test).....	3.7	80%	3.0	0	0	11	4	1.6
		5.0	90%	9.5	4	3	....	...	...
8	Negative (patch test).....	4.4	100%	3.9	0	0	11	3.2	5.0
		5.3	....	6.8	4	6	....	...	...
9	Negative.....	4.7	99%	3.4	1	1	....	...	...
		5.4	112%	7.5	11	5	....	...	...
10	.....	3.7	75%	11.0	..	..	....	...	...
				14.0					
11	Negative (0.00002 mg.).....	3.9	95%	5.1	0	0	10.5	...	4.0
		4.8	96%	10.0	4	1	....	...	...
12	Negative.....	5.2	....	5.4	..	..	....	...	...
13	Negative (patch test).....	3.7	71%	7.6	1	0	9.5	3.0	...
		4.5	83%	15.3	8	7	....	...	...
14	Negative (patch test).....	4.0	81%	4.7	0	0	10.5	3.6	5.7
		4.5	85%	6.6	8	2	....	...	...
15	Positive (weak).....	...	....	5.3	2	4	....	...	...
16	Negative.....	5.5	110%	7.1	7	0	8.5	5.4	1.4
		...	....	7.2	8	..	11.5	8.9	3.1
17	Negative (patch test) and test with purified protein derivative.....	2.6	55%	9.9	2	0	11.2	5.5	...
		3.3	73%	19.3	9	2	....	...	...
18	2+ positive (0.00002 mg.)....	4.9	13 Gm.	5.8	2	0	9.7	2.9	8.0
		...	14 Gm.	8.8	6	7	....	...	...
19	Negative (0.00002 mg.).....	4.2	11.5 Gm.	8.5	0	0	8.5	3.8	8.8
		4.6	12 Gm.	10.9	6	6	9	...	10.2
20	2+ positive (0.000002 mg.)...	4.9	92%	6.0	0	2	11.0	3.1	9.2
		...	95%	6.4	7	4	....	...	...
21	Negative (.000002 mg.).....	4.2	85%	4.5	0	1	11.8	3.2	6.8
		4.6	96%	8.4	13	6	....	...	...
22	Negative (patch test) and test with purified protein derivative.....	4.0	13.6 Gm.	6.2	0	0	....	...	...
		5.1	14.5 Gm.	11.3	5	5	....	...	...
23	Negative (patch test).....	...	....	...	5	..	10.5	5	6
24	Negative (patch test).....	4.7	100%	8.4	12	3	....	...	...
25	Negative (patch test) and test with purified protein derivative.....	5.0	98%	5.0	1	0	....	...	...
		...	105%	6.0	4	0	....	...	...
26	Negative (patch test).....	...	....	...	..	..	....	4	4.4
27	Negative (0.00002 mg.).....	4.0	85%	5.2	0	0	10.6	3.4	...
		5.9	102%	9.6	12	7	....	...	...
28	Negative (patch test) and test with purified protein derivative.....	4.4	87%	4.6	3	3	....	...	...
		5.5	105%	9.0	5	7	....	...	...

* When several determinations were made the high and low values are given.

noted by many writers. It has led to the theory that sarcoidosis is an atypical response of the reticuloendothelial system to the tubercle bacillus. In Reisner's [8] series the incidence of positive reactions was 40 per cent; however, when a positive reaction does occur it is usually weak and occurs only with the higher concentrations of tuberculin. Reisner tested 10 patients with 10 mg. of old tuberculin and obtained negative reactions in all. The tuberculin test should always be done and is of some value in the differential diagnosis. Another interesting and significant symp-

Laboratory Observations Continued—Table 2-A

Case	Albumin, Gm.	Globulin, Gm.	Miscellaneous Laboratory Tests
1	3.8 5.0	2.9 3.0	Sedimentation rate elevated
2	3.5	5.2	Agglutination test for brucellosis gave a negative reaction
3	4.0 3.1	3.9 2.9	Sedimentation rate elevated
4	4.7	3.3	Spinal fluid sterile
5	3.6 4.5	3.0 1.5	.....
6	5.5 4.1 4.1	3.4 5.1 2.1	Cholesterol content 184 mg.
7	4.0 4.4 5.5 4.7	2.9 3.6 2.5 2.0	Reaction to test for heterophile antibodies negative
8	4.6 4.3	3.4 3.7	Cholesterol content 194 mg.
9	4.3 4.5 5.5	1.4 2.3 1.4	Reaction to test for heterophile antibodies negative; agglutination test for brucellosis gave a negative reaction
10	...	...	.....
11	5.2 4.6	2.1 2.7	Agglutination test for brucellosis gave a negative reaction; sedimentation rate elevated
12	4.7	3.9	Sedimentation rate elevated
13	4.4 4.3	3.3 4.0	Sedimentation rate elevated; reaction to test for heterophile antibodies positive (3+ [1:112], 1+ [1:224])
14	4.4	3.6	Agglutination test for brucellosis gave a negative reaction, as did the test for heterophile antibodies; sedimentation rate elevated

tom, when present, is the elevation of the globulin fraction of the blood protein (table 2). A study of the blood protein was carried out in 27 of the 28 cases by the standard method of digestion and nesslerization. If the figures given for average normal by Peters and Van Slyke are followed [32] (total protein 7 Gm. per hundred cubic centimeters, with albumin 4.44 Gm. and globulin 2.58 Gm.), the total protein was above this figure in 19 and the globulin level elevated in 23 patients. It is interesting in this connection that elevation of the globulin fraction of the blood protein has been described in diseases associated with pro-

32. Peters, J. P., and Van Slyke, D. D.: Quantiative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. I.

liferation of the reticuloendothelial system. This is notably true in lymphogranuloma venereum, multiple myeloma and kala-azar. The Frei test gave a negative reaction in the 4 instances in which it was done.

An elevation of the blood calcium and alkaline phosphatase levels in sarcoidosis was described by Harrell and Fisher.[33] The calcium content was determined by the Clark-Collip modification of the Kramer-Tisdall method in 16 patients, and it was above 10.5 mg. in 10 (table 2). It should be noted that 8 of these also had hyperproteinemia. This elevation may be due to the calcium-binding power of the blood proteins, as discussed by Jaffe and Bodansky.[34] Fourteen determinations of the alkaline phosphatase of the blood were made by the modified King-Armstrong method. In only 5 instances were the readings higher than 6 Bodansky units, the highest single figure being 10.2 Bodansky units.

Laboratory Observations Continued—Table 2-B

Case	Albumin	Globulin	Miscellaneous Laboratory Tests
15	4.3 4.5	2.4 2.7	Agglutination test for brucellosis gave a negative reaction
16	4.1 5.4	2.2 3.4	Sedimentation rate normal; coccidioidin test gave a negative reaction
17	3.3 4.0	5.2 3.3	Reaction to the cephalin flocculation test was positive (3+)
18	3.4 4.4 3.9	3.4 2.4 3.0	Sedimentation rate normal; test for heterophile antibodies and agglutination test for brucellosis gave negative reactions
19	3.6 3.5 4.7 3.5	4.3 2.4 3.1 4.3	Reactions to the test for heterophile antibodies and to the coccidioidin and Frei tests were negative
20	5.2 4.0	3.2 2.2	Sedimentation rate normal; Frei test, test for heterophile antibodies and coccidioidin test gave negative reactions
21	3.0 3.4	3.7 3.5	Sedimentation rate normal
22	5.0	2.5	Agglutination test for brucellosis, test for heterophile antibodies and coccidioidin test gave negative reactions
23	4.4	3.6	Reactions to test for heterophile antibodies and to the Frei test were negative
24	3.7	2.5	Test for heterophile antibodies gave a negative reaction
25	2.8 3.9	3.7 2.8	Cholesterol content 264 mg., esters 73.9%; reaction to the test for heterophile antibodies negative; sedimentation rate normal
26	4.1	2.1	Test for heterophile antibodies gave a negative reaction; cholesterol content 240 mg.
27	4.3	2.7	Reaction to the Frei test was negative
28	4.4 4.4 3.5	2.4 2.8 3.3	Sedimentation rate elevated; agglutination test for brucellosis gave a negative reaction

33. Harrell, G. T., and Fisher, S.: Blood Chemical Changes in Boeck's Sarcoid with Particular Reference to Protein, Calcium and Phosphatase Values, J. Clin. Investigation **17**:687-691, 1939. Harrell, G. T.: Generalized Sarcoidosis, J. Bowman-Gray School Med. **1**:1-4, 1943.

34. Jaffe, H. L., and Bodansky, A.: Serum Calcium; Clinical and Biochemical Considerations, J. Mt. Sinai Hosp. **9**:901-920, 1943.

Total and differential white blood cell counts were recorded one hundred and eight times in the 28 cases (table 2). Of these counts, only ten were below 4,500 cells. Only 7 patients had any single count below this figure, and in them it was not consistently low. Thus 21 patients showed no leukopenia. The great majority of the blood counts were normal, with elevations from time to time during the course of the disease, usually with some intercurrent infection. This finding differs somewhat from that of Reisner,[8] who found leukopenia in one third of his cases; 16 of Longcope's [28] 28 patients had counts between 3,000 and 6,000. Longcope and Pierson [35] have described eosinophilia. In our series 7 patients had an eosinophil count of 5 per cent or more, while in 5 instances single counts of 10 per cent or above were recorded. The monocytes were not consistently increased as has been reported by Harrell,[12] although occasionally single counts as high as 9 to 12 per cent were seen. One patient (case no. 1) who died and on whom necropsy was performed was followed over a period of one year. He showed in a total of twelve white blood cell counts no significant deviation from normal in any value except for one total leukocyte count of 13,000, which occurred during a febrile period associated with hemoptysis. A total of eighty-two determinations of the red blood cell count and the hemoglobin content were made in the 28 cases. In only 2 was the erythrocyte count below 4,000,000 (cases 3 and 17). In 1 of these (case 17), the patient, a man 58 years of age, had previously undergone splenectomy for acquired hemolytic jaundice.

A few other laboratory observations showed no significant changes. The agglutination test for brucellosis elicited a negative reaction in 8 patients, and the reaction to the coccidioidin skin test was negative in 5. The agglutination test for heterophile antibodies was done in 12 patients, and the reaction was negative in 11; 1 patient had a slightly positive reaction. In the majority of the patients studies of sputum and gastric washings for tuberculosis and fungi were made, and in all instances the results were negative. Inoculation of animals for tuberculosis was not done. There was no instance of an increase in the nonprotein nitrogen or blood cholesterol. No Bence Jones protein was found in the urine. The Kahn test was performed on all patients in this series and elicited a negative reaction in all except 1, who presented clinical evidence of syphilis. This is in contrast to Reisner's [8] series, in which the reaction to the Wassermann test was positive ten times and doubtful twice in 35 patients. This led him to believe that the disease might account for a false positive reaction, which conclusion we were unable to confirm. The sedimentation rate was determined in 12 patients and found to be increased in 8.

35. Longcope, W. T., and Pierson, J. W.: Boeck's Sarcoid (Sarcoidosis), Bull. Johns Hopkins Hosp. **60**:223-296, 1937.

ROENTGENOLOGIC STUDY

In all 28 patients there was evidence of intrathoracic lymphadenopathy (table 3). Its presence is not always easily detectable. Examination should include careful roentgenoscopy, with a swallow of barium given to the patient during the course of the study. A posteroanterior

TABLE 3.—*Roentgenologic Observations*

	Intrathoracic Lymph Nodes*						
	Paratracheal		Peribronchial				
Case	Right Side	Left Side	Right Side	Left Side	Types of Pulmonary Infiltration*		Involvement of Hands*
1	+	+	+	+	++	Reticular and nodular	++
2	+	0	++	++	0	.....	0
3	++ —)0	+ —)0	++ —)0	++ —)0	+	Reticular	++
4	++	++	++	++	+	Reticular and nodular	0
5	+	+	+	+	+	Nodular	++
6	++	+	+	+	0	Pleural, with interlobar effusion	0
7	++	++	++	++	0	.....	0
8	++	+	++	++	+	Reticular	0
9	++ —)+	++ —)+	++ —)+	++ —)+	0	.....	0
10	+	+	+	+	0	Pericarditis and pleural effusion	0
11	++	+	+	+	0	.....	0
12	+	+	+	+	0	.....	Not examined
13	++	+	++	++	+	Nodular and reticular	0
14	++	+	0	0	0	.....	0
15	++	+	+	+	+	Reticular	0
16	+	0	0	0	++	Reticular and nodular	0
17	++ —)++	+ —)++	+	+	+	Reticular	+
18	+	0	++	++	0	.....	0
19	+	+	++	++	++	Reticular and nodular	0
20	+	+	++	++	0	.....	0
21	+	0	++	++	0	.....	+
22	++	0	++	++	+	Reticular	0
23	++	++	++	++	+	Reticular	0
24	+	+	+	+	+	Reticular and nodular	0
25	++	++	++	++	0	.....	0
26	++	+	++	++	0	.....	0
27	+	0	0	0	+	Reticular and nodular	0
28	++	+	+	+	+	Reticular and nodular	+

* 0 indicates absent, + slight to moderate, ++ pronounced and — change while under observation.

and lateral examination should be made, together with such oblique views as are deemed necessary. A Bucky-Potter diaphragm will aid in the delineation of the trachea and the major bronchi, and a laminagram may be of value in selected cases. With this careful technic, nodes of 2 cm. in diameter or greater will be detected. Nodes smaller than this will most likely not be seen even with the best technic available at the present time because of the density of the overlying structures. In our

series the individual nodes varied in size from 2 to 5 cm. in diameter. Only occasionally were they larger than this. The increase in size of the paratracheal group parallels that of the peribronchial group. The bifurcation group of glands is probably similarly enlarged, but this is difficult to demonstrate. Bilateral involvement is the rule. Like the peripheral nodes, the intrathoracic nodes tend to remain discrete and do not have a tendency to coalesce. Pathologically, too, it has been noted that the sarcoid process has little tendency to break through the capsule. Consequently, in the roentgenogram the tumor will show a lobulated border because of the overlap of the adjacent nodes, giving strong evidence that it consists of a group of enlarged lymph nodes (fig. 4).

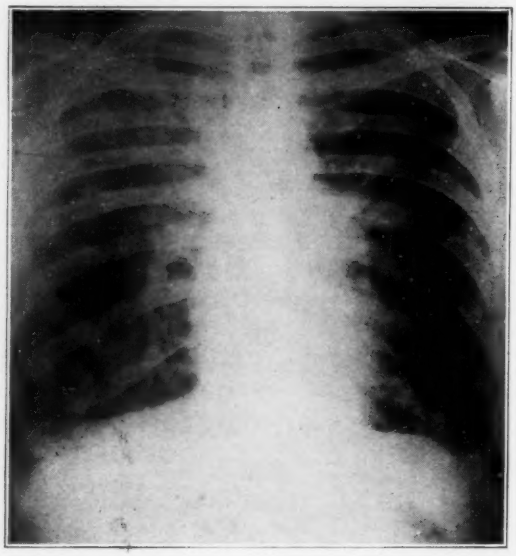

Fig. 1 (case 1).—Extensive nodular and reticular changes are seen throughout both pulmonary fields, and there is a slight enlargement of both the peribronchial and the paratracheal lymph nodes. The pulmonary parenchymal involvement became progressively more extensive and resulted in the development of failure of the right side of the heart, with death of the patient.

There was only 1 exception to this rule in our series, and as a result we were led to believe that it was a malignant process (fig. 5). Calcification in or about the nodes was also noted only once (fig. 2). This is interesting in view of the fact that Schaumann [3] expressed the opinion that its presence indicates tuberculosis rather than sarcoid. The absence of calcification is of value in ruling out a multilocular dermoid cyst of the anterior mediastinum. In several patients we have been able to demonstrate a slight narrowing of the trachea or of one of the major

bronchi (fig. 8), but in no instance was there evidence of lobar collapse. Although the esophagus may be compressed or displaced by the mediastinal mass, there was no involvement of the esophageal wall in our series. In no case was there evidence of involvement of the phrenic nerves. Diaphragmatic paralysis is not an unusual occurrence in carcinoma of the lung, with spread to the peribronchial lymph nodes, and its absence helps to exclude bronchiogenic carcinoma.

With involvement of the intrathoracic lymph nodes, the differentiation of the relatively benign disease of sarcoid from the malignant forms of lymphogranuloma must be made. It should be clearly noted that enlargement of the right paratracheal nodes or group of nodes is of no value in making the differential diagnosis, as was once proposed (Kirklin and Hefke,[36] Wessler and Greene [37] and Williams [38]). It will be seen with equal frequency in both types of lesion (fig. 9). Our experience has been confirmed by others (Wolpau, Higley and Hauser [39]). However, in 11 of our cases the lymph nodes on the right

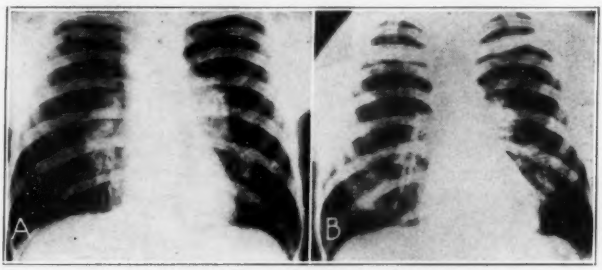

Fig. 2 (case 3).—*A*, roentgenogram taken on April 14, 1945, when the patient first appeared in the hospital. There is decided enlargement of the peribronchial and paratracheal lymph nodes. A fine reticular infiltration is present throughout both pulmonary fields. The unusual finding of calcification within the lymph nodes is present. *B*, eleven months later there has been a considerable regression of the peribronchial lymph nodes, suggesting a fibrous tissue replacement. The reticular pattern in both fields has been replaced by a gross nodularity.

side of the chest were larger and more numerous than those on the left. The reason for this is not apparent. It may be explained on the basis of the anatomic finding of Sukiennikow [40] that the nodes on the

36. Kirklin, B. R., and Hefke, H. W.: Roentgenologic Study of Intrathoracic Lymphoblastoma, Am. J. Roentgenol. **26**:681-690, 1931.

37. Wessler, H., and Greene, C. M.: Intrathoracic Hodgkin's Disease: Its Roentgen Diagnosis, J. A. M. A. **74**:445-448 (Feb. 14) 1920.

38. Williams, E. R.: Radiological Study of Intrathoracic Lymphogranuloma and Lymphosarcoma, Brit. J. Radiol. **8**:265-279, 1935.

39. Wolpau, S. E.; Higley, C. S., and Hauser, H.: Intrathoracic Hodgkin's Disease, Am. J. Roentgenol. **52**:374-388, 1944.

40. Sukiennikow, W.: Topographische Anatomie der bronchialen und trachealen Lymphdrüsen, Berlin 1903; cited by Miller.[41]

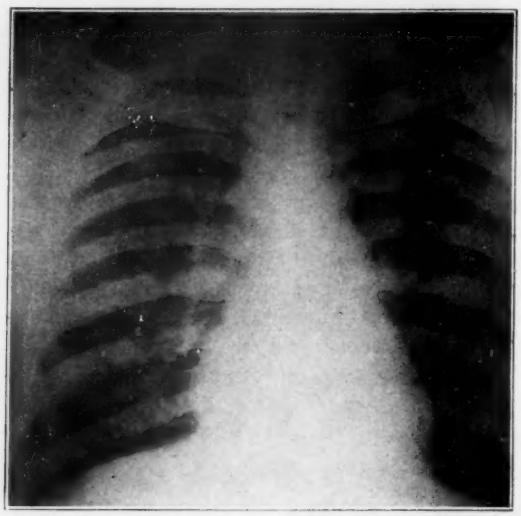

Fig. 3 (case 5).—Bilateral enlargement of the paratracheal and peribronchial lymph nodes is present, with a heavy, coarse, irregular infiltration scattered throughout both pulmonary fields.

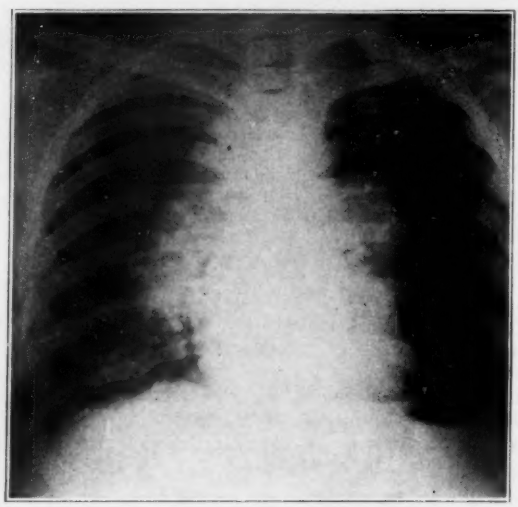

Fig. 4 (case 8).—Pronounced enlargement of the paratracheal and peribronchial lymph nodes is noted. There is a fine reticular infiltration throughout both pulmonary fields.

right side are greater in number than those on the left in the normal subject. This observation was confirmed by Miller,[41] who also noted that there were a greater number of lymph nodes about the epiarterial bronchus than about the bronchi supplying the middle and lower lobes of the right lung.

Enlargement of the intrathoracic lymph nodes is found in the vast majority of cases of sarcoidosis. It was present in all our 28 cases, in 30 of 35 cases reported by Reisner[8] and in 30 of 31 cases reported by Longcope.[28] In contradistinction, intrathoracic lymphadenopathy is a less frequent finding in malignant lymphoma, the incidence varying from 23 per cent (clasmatocytic type) to 61 per cent (Hodgkin's type) in a series of 618 cases studied by Gall and Mallory.[42] Thus in a patient with enlargement of the peripheral lymph nodes the absence of involvement of intrathoracic lymph nodes on roentgen study favors a diagnosis of malignant lymphoma rather than of sarcoid.

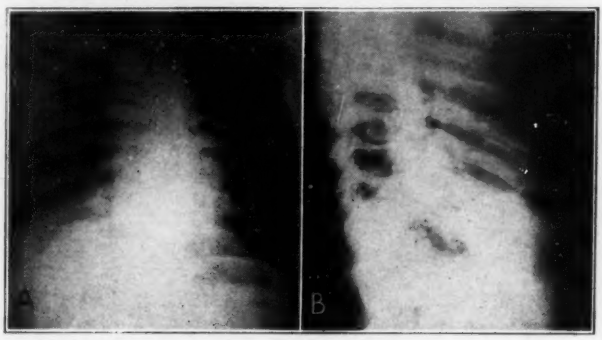

Fig. 5 (case 6).—Posteroanterior and lateral views show a soft tissue tumor in the anterior-superior mediastinum. This is more prominent on the right side. The margins are straight, and the serrated border indicating a cluster of lymph nodes, usually seen in sarcoid, is missing. Also, there is evidence of fluid in the base of the right lung, with some fluid in the interlobular fissure and a slight degree of compression atelectasis of the lower lobe. The coalesence of the lymph nodes seen only in this patient led us to the erroneous conclusion that this was a malignant lymphoma.

In our experience the lymph nodes tend to remain discrete, presenting a well defined border. Later in the course of the disease the nodes regress slowly and spontaneously, to be replaced by fibrous tissue (figs. 2, 6 and 8). This impression of fibrous tissue replacement has been confirmed in cases coming to necropsy (Rubin and Pinner,[8] Schu-

41. Miller, W. S.: The Lung, Springfield, Ill., Charles C Thomas, Publisher, 1937, chap. 8.

42. Gall, E. A., and Mallory, T. B.: Malignant Lymphoma, Am. J. Path. **18**:381-429, 1942.

mann [3] and Cotter [43]). In malignant lymphoma, however, the malignant process will tend to break through the capsule and invade the surrounding structures (Jackson and Parker [44]), and hence the clearcut outline of the enlarged nodes is soon lost. Spontaneous regression of malignant lymphoma untreated by radiation can occur, but it is rare. Cavitation of the lung and the formation of bronchoesophageal fistula will occur in advancing Hodgkin's disease (Vieta and Craver [45]), but these have not been found in uncomplicated sarcoidosis.

The roentgenographic appearance of the chest in erythema nodosum and sarcoidosis is similar. When intrathoracic lymphadenopathy is the only manifestation, it is impossible to distinguish between them by roentgen study alone (Paul and Pohle [46] and King [24]), and a possible common etiologic relationship has been suggested by Kerley [47] and Vogt.[48] Although we have had no experience with pulmonary coccidioi-

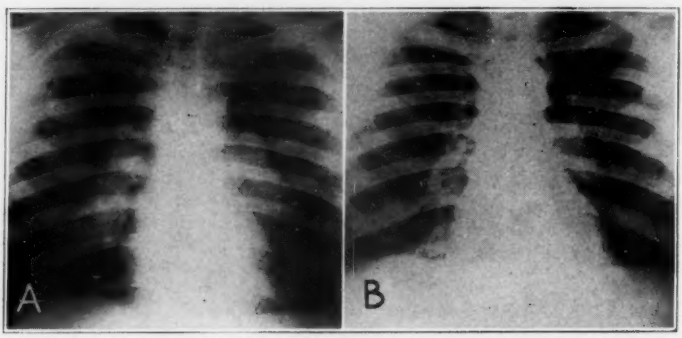

Fig. 6 (case 9).—*A*, on April 21, 1945 decided enlargement of the paratracheal and peribronchial lymph nodes was noted when the patient complained of a slight cough. He had been admitted to the hospital for a battle wound. These lymph nodes remained discrete, with well defined borders. This appearance is strongly suggestive of sarcoidosis. *B*, on Feb. 18, 1946, ten months later, the enlarged lymph nodes have undergone almost complete spontaneous regression, with fibrous tissue replacement. A faint, strandlike infiltration is now noted throughout both pulmonary fields.

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43. Cotter E. F.: Boeck's Sarcoid: Autopsy in Case with Visceral Lesions, Arch. Int. Med. **64**:286-295 (Aug.) 1939.

44. Jackson, H., and Parker, F.: Hodgkin's Disease: II. Pathology, New England J. Med. **231**:35-43, 1944.

45. Vieta, J. O., and Craver, L. F.: Intrathoracic Manifestations of Lymphomatoid Diseases, Radiology **37**:138-158, 1941.

46. Paul, L. W., and Pohle, E. A.: Mediastinal and Pulmonary Changes in Erythema Nodosum, Radiology **37**:131-137, 1941.

47. Kerley, P.: Significance of Radiologic Manifestations (in Chest) of Erythema Nodosum (Relation to Sarcoidosis), Brit. J. Radiol. **15**:155-165, 1942.

48. Vogt, J. H.: Tuberculin Negative Erythema Nodosum, Acta med. Scandinav. **123**:151-153, 1946.

domycosis in the hospital in which this study was made, there are several reports in the literature which indicate that these two diseases may be confused (Kerley [47]). Mediastinal lymphadenopathy will occur in coccidioidomycosis, being present in one sixth of all cases in which the disease is in the primary stage and in two thirds of those in which it is in the progressive stage (Lee, Nixon and Jamison [49]). However, the thin-walled cavities in the lung described in coccidioidomycosis [49]

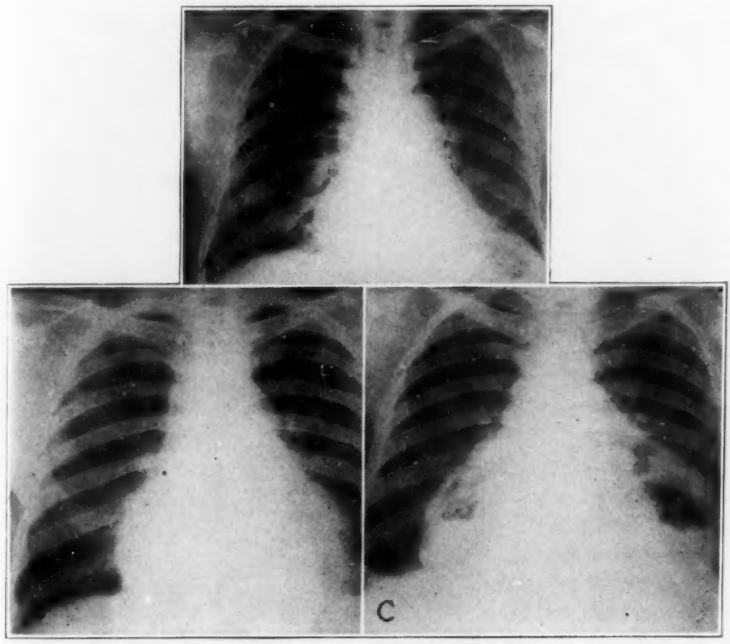

Fig. 7 (case 10).—*A*, on April 23, 1943, there was bilateral enlargement of the paratracheal and peribronchial lymph nodes, with slight enlargement of the heart. *B*, on April 30 there has been a further increase in the size of the heart. It is globular in shape, and a zone of semitranslucency is seen about it. This is more marked about the left border. It was interpreted as pericardial fluid. *C*, on September 10 a pericardial aspiration was performed and air injected into the pericardium. Fluid levels are noted on both sides of the heart, with considerable thickening of the pericardium.

have not been seen in these cases of sarcoid. A history of residence in an area in which the disease is endemic, a positive reaction to the skin

49. Lee, R. V.; Nixon, N., and Jamison, H. W.: Syllabus on Coccidioidomycosis, Coccidioidomycosis Control Program for the Army Air Force Western Training Command, Headquarters Army Air Forces Western Flying Training Command, March 15, 1944.

test for coccidioides infection or the culture of the fungus from the sputum would aid in making the differential diagnosis

In this study the earliest manifestation of the disease seemed to be enlargement of the intrathoracic lymph nodes. After a variable length of time, these tend to regress spontaneously, while parenchymal involvement apparently increases (figs. 2, 6 and 8). For this reason some authors have postulated a retrograde lymphatic spread (Bruce and Wassen [23] and Castleman [50]), although Miller [41] in his excellent study

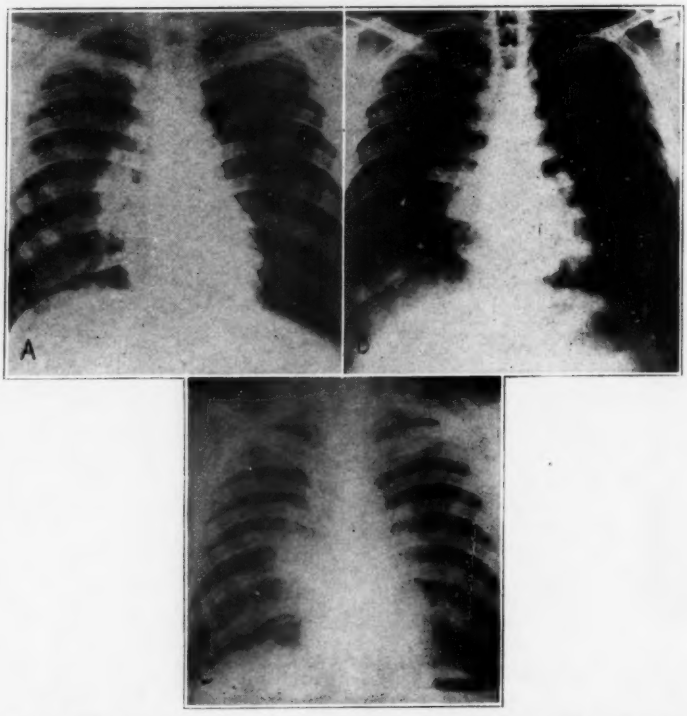

Fig. 8 (case 13).—*A*, on the first examination, on July 16, 1945, enlargement of the paratracheal and peribronchial lymph nodes is noted. *B*, an overexposed film made with a Bucky-Potter diaphragm shows narrowing of the lower lobe of the right lung, probably due to compression of the enlarged lymph nodes. However, atelectasis as a result of bronchial compression was not found in this series. *C*, on September 7 the enlarged lymph nodes showed beginning fibrosis, and a reticular and nodular infiltration was then noted in both pulmonary fields.

makes the unequivocal statement that an ebb and flow of the lymph does not occur, this being effectively prevented by the valves of the lymphatic

50. Sarcoid of Mediastinal Lymph Nodes, Cabot Case 30331, New England J. Med. **231**:268-269, 1944.

vessels which point toward the hilus. Pulmonary changes in sarcoid frequently pose a difficult problem in diagnosis. About equal involvement of both lungs is the rule. As was first shown by Schaumann,[3] the changes are limited to the lymphatic vessels and lymphoid tissues of the reticuloendothelial system. The lungs are abundantly supplied with lymphoid tissue.[41] This lymphoid tissue is in close association with the bronchi, blood vessels and pleura; consequently, no definite pattern of the changes in sarcoidosis can be predicted. Furthermore, the appearance of the chest at any one time will depend on the stage of the disease. The statement of Kirklin and Morton[51] that the middle and lower thirds of the pulmonary fields are usually infiltrated has not been borne out in our series in which changes in the upper third of the lungs were noted with equal frequency.

Pulmonary parenchymal involvement was seen in 15 of the 28 cases (table 3). This is not a reliable index of the incidence of parenchymal involvement in sarcoidosis, as the period of observation in some of our patients was limited to a few months. The true incidence may be much higher than this, parenchmyal involvement being seen in 33 of 35 cases reported by Reisner.[8] The involvement is of two main types, which are frequently coexistent. The first and commonest is a reticular type, with thin strandlike areas of increased density extending out from the hilus (figs. 2*A*, 4 and 6*B*). This type was seen in all but 1 of the cases with parenchymal involvement recognizable roentgenographically. It probably represents involvement of the interlobular lymphatic vessels, as in the patient on whom autopsy was performed by Schaumann.[3] It must be differentiated from a lymphatic spread of pulmonary metastases, pulmonary congestion secondary to cardiac failure and silicosis. Mueller and Sniffen[52] showed that lymphangitic carcinomatosis is usually characterized by an irregular network of increased density in which are interspersed numerous small nodules. In congestive heart failure the basal portion of the lung is most heavily involved. Enlargement of the paratracheal lymph nodes is rare in silicosis, and an occupational history would aid in ruling out this disease. Less frequently a nodular increase in density throughout both pulmonary fields is observed; it was noted in 9 of 15 cases (figs. 1, 3 and 9*B*). These nodules are of variable size and slightly irregular in outline. The slight irregularity of the nodules is not due to an inflammatory reaction, which is generally absent, as shown by the postmortem studies of Rubin and Pinner.[6] At this stage the disease may be confused with miliary tuberculosis. In the

51. Kirklin, B. R., and Morton, S. A.: Roentgenological Changes in Sarcoid and Related Lesions, Radiology **16**:328-331, 1931.

52. Mueller, H. P., and Sniffen, R. C.: Roentgenologic Appearance and Pathology of Intrapulmonary Lymphatic Spread of Metastatic Cancer, Am. J. Roentgenol. **53**:109-123, 1945.

latter the densities tend to be more discrete and more uniform in size, since they are the result of a shower of infected emboli. In sarcoid the lesions are less numerous and more widely spaced.

Owing to the predilection of the disease for the reticuloendothelial system, there must result considerable obstruction to the normal lymph flow in the lungs, with a corresponding disturbance of pulmonary physiology. Bruce and Wassen [23] found a uniform reduction in the vital capacity in their 6 cases, but they felt that this reduction was too small to explain the dyspnea from which their patients suffered. They believed that a thickening and narrowing of the walls of the blood vessels, as described by Schaumann [3] and by Tice and Sweany,[26] is the more important factor. One death occurred in this series (case 1), and it was attributed to respiratory embarrassment, with resultant failure of the right side of the heart (fig. 1). Endarteritis of the pulmonary vessels, however, was not found in this patient. Although the mortality rate among patients with sarcoid is low, this has not been an uncommon sequence of events in the cases studied pathologically to date (Rubin and Pinner,[6] Bernstein and Oppenheimer [53] and Longcope and Fisher.[16] However, it should be reiterated that we were unable to correlate the degree of pulmonary involvement with the severity of symptoms in our series (fig. 9*B*).

Involvement of the heart and its covering is not unknown (Longcope and Fisher,[16] Salvesen,[54] Cotter [43] and Schaumann [3]). In 1 of our patients (case 10) a pericardial effusion developed, and it was necessary to aspirate the pericardial sac on four occasions (fig. 7). In only 2 of our patients did a pleural effusion develop, and in neither was it extensive (figs. 5 and 7). With the known involvement and subsequent blockage of the pulmonary lymphatic vessels, it seems unusual that this complication does not occur more frequently. In none of the patients was involvement of the bony thorax noted. This may be of value in differentiating the malignant conditions with which sarcoid may be confused.

The hands and feet were examined in 27 patients. Of these, 6 had indisputable lesions in the hands and 1 was considered as having questionable changes, an average of 22 per cent with indicative signs. No lesions were found in the feet or in any of the long bones when they were examined, although they have been reported by others (Reisner [8] and Longcope [28]). The presence of skeletal involvement is thought to be strongly suggestive of sarcoid, and even with a low incidence of 22 per cent a routine examination of the hands in suspected cases would

53. Bernstein, S. S., and Oppenheimer, B. S.: Boeck's Sarcoid: Report of Six Cases with One Necropsy, J. Mt. Sinai Hosp. **9**:329-343, 1942.

54. Salvesen, H. A.: The Sarcoid of Boeck: A Disease of Importance to Internal Medicine, Acta med. Scandinav. **86**:127-151, 1935.

be justified because of its diagnostic value. None of the 6 patients had any symptoms referable to the bony changes, which were picked up on routine examination. The osseous involvement appears to be of two types, which, however, may be coexistent. The first is a diffuse rarefaction, with a reduction in the number of the bony trabeculae in the medullary portion of the bone and a slight thinning of the cortex (fig. 11 *B* and *C*). The other type consists of small oval defects, usually found at the heads or bases of the middle and proximal phalanges (fig. 11 *A*). Jüngling [55] called these oval cystoides or cystlike. They are not true cysts but replacements of bone by small granulomas (Ellis [56]). In the hands, sarcoid must be differentiated from tuberculous dactylitis, gout and leprosy. In tuberculous dactylitis there is a notable swelling of the soft tissue, destruction of bone and sinus formation, and occasionally the joint is involved. We have not seen this type of a reaction, but if sarcoid should prove to be an atypical type of tuberculosis this differential would be pointless. The foci of bone destruction in gout are

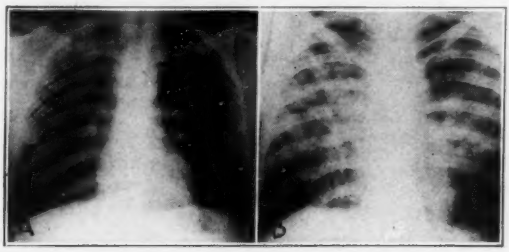

Fig. 9.—*A* (case 14), in this patient the discoverable enlargement of lymph nodes is limited to the paratracheal group, and this is more marked on the right side. Previous writers have considered this to be pathognomonic of Hodgkin's disease, but it appears that this was not so in our series. *B* (case 16), there is pronounced nodular and reticular infiltration throughout both pulmonary fields; yet this patient was asymptomatic, and the disease was discovered on routine examination of the chest. It illustrates the frequently made observation that in sarcoid the severity of the pulmonary symptoms is not related to the extent of pulmonary involvement.

more likely to be clearcut, punched-out areas usually in the metatarsals and phalanges, and a diffuse rarefaction of the bone as seen in sarcoid is not usual. Leprosy is usually accompanied by changes which are due to vascular insufficiency, as indicated by a progressive loss of bone substance beginning in the distal phalanges and progressing proximally. Since the bone marrow comprises a considerable portion of the reticuloendothelial system, it is surprising that osseous lesions do not occur

55. Jüngling, O.: Ostitis tuberculosa multiplex cystica, Fortschr. a. d. Geb. d. Röntgenstrahlen **27**:375, 1920. Footnote 4.

56. Ellis, F. A.: Jungling's "Ostitis Tuberculosa Multiplex Cystoides" Is Not Cystic Tuberculous Osteitis, Acta med. Scandinav. **104**:221-223, 1940.

more frequently. It may be that in the majority of cases the lesions are too small or too diffuse to cause recognizable alterations in the osseous structures. In no instance has involvement of the joint been found except for calcification in the periarticular tissues of the metacarpophalangeal joints of 1 patient. In the case of 1 adolescent patient of 13 years of age in whose hands osseous lesions were found we wondered whether these lesions might interfere with epiphysial growth, but a follow-up study indicated that epiphysial development was proceeding normally. A longitudinal striation of the finger nails has been described in association with the osseous lesions of sarcoid (Harrell [12]), but we have not observed it.

TREATMENT

It is not the purpose of this paper to discuss the treatment of sarcoid. However, the question of treatment of intrathoracic lymphadenopathy by high voltage roentgen therapy is often raised. In 2 of our patients a test dose of 1,300 r. was given, with the use of 220 kilovolts and 15 milliamperes, a 50 cm. distance and a half-value layer of 1.34 mm. of copper. In neither of these cases was there an observable reduction in the size of the lymph nodes or an alteration of the clinical course of the disease. The value of this dose of radiation as a therapeutic test is in itself open to question. The pulmonary manifestations are known to regress spontaneously, and if this occurred simultaneously with the administration of deep radiation it might lead to an erroneous conclusion.

REPORT OF CASES

CASE 1.—It seems worth while to report in detail the only case which came to necropsy. The patient was a Negro, 26 years of age, who first noted mild shortness of breath and cough in June 1942. Because of increase in these symptoms, he was hospitalized on June 12 when a diffuse infiltration of both lungs of unknown cause was discovered. The only physical signs were slight impairment of the percussion note and medium and fine moist rales at the bases of both lungs. The paucity of signs was in striking contrast to the roentgen study of his chest, which showed nodular areas of increased density throughout all portions of both pulmonary fields (fig. 1). Roentgenograms of the hands showed the typical lesions of sarcoid (fig. 11). There was no involvement of the skin or superficial lymph nodes. The sputum was sterile on repeated culture, and smears for fungi and acid-fast bacilli were negative. The gastric washings were likewise sterile. A blood count and urinalysis were noncontributory. The total protein varied between 6.7 and 8 Gm. per hundred cubic centimeters, and the highest globulin level was 3 Gm. The sedimentation rate was 38 mm. in one hour (Wintrobe).

Ambulatory and afebrile on his admission to the hospital, the patient gradually grew worse until December 29, when he became cyanotic and dyspneic, coughed up a little blood and had a low grade fever for several days, the maximum temperature being 100.6 F. He was given sulfadiazine for about three weeks, after which he improved and the temperature became normal. From this time on he became increasingly cyanotic, and oxygen was needed most of the time until he finally died on May 29, 1943, a little less than a year from the date of his first symptoms.

At necropsy the chief feature of interest were the lungs, the right lung weighing 1,750 Gm. and the left 1,510 Gm. They were exceedingly firm throughout, the pleural surface was smooth and there were no adhesions. On section, a diffuse, firm cellular infiltration of greenish gray color was seen throughout, leaving extremely little normal pulmonary tissue. This gray cut surface seemed to be composed of innumerable nodules which had coalesced. There was no cavitation or necrosis. The hilar lymph nodes, enlarged to a diameter of 5 by 3 cm., were firm and showed a greenish gray cut surface. There were gray granulomatous nodes in the liver and spleen, these organs weighing 1,740 Gm. and 240 Gm. respectively. The weight of the heart was 400 Gm., with hypertrophy, particularly of the right ventricle. The wall of the left ventricle measured 1.6 cm. and the wall of the right ventricle 1.2 cm. in thickness. There was no gross evidence of involvement of the cardiac muscle or pericardium. Microscopic study of multiple sections showed the normal pulmonary tissue almost entirely replaced by a granulomatous process. There were innumerable nodular aggregates of epithelioid cells and many multinucleated giant cells. The giant cells had a tendency to contain more nuclei and to show a somewhat different configuration from those seen in the spleen and liver. All other organs and tissues, including the brain, pituitary, thyroid, heart, pancreas, kidneys, adrenals, prostate, testicles and vertebral bone marrow, were free from the process.

CASE 3.—The patient was a 13 year old white girl who had fever, a weight loss of 25 pounds (11 Kg.) and severe anemia. She had had fever for six weeks before she was seen at the hospital in December 1944. This patient showed the most widespread involvement of various organs that we have seen. There were bilateral uveitis and keratitis, bilateral parotitis and enlargement of the submaxillary glands. Transient paralysis of the right side of the face, due to the parotid swelling, developed. Generalized lymphadenopathy and extreme anemia were found. There was involvement of the bones of the hands (fig. 11). The spleen and liver were palpable, and urinalysis repeatedly showed albuminuria, occasional red cells, many pus cells and many hyaline and granular casts. The reaction to the tuberculin test was negative. The total protein was 7.9 Gm. per hundred cubic centimeters, with globulin 3.9 Gm. The sedimentation rate was 34 mm. A roentgenogram of the chest revealed enlargement of the peribronchial and paratracheal lymph nodes, with a fine reticular infiltration of both lungs when first seen (fig. 2 *A*). Biopsy of the right epitrochlear node showed typical epithelioid tubercles, with giant cells characteristic of sarcoid. The patient improved considerably under general care, rest, diet and administration of vitamins and iron. When last seen, in February 1946, she was much improved, the anemia had been corrected, she had gained weight and the lymph nodes in the chest had decreased in size, leaving only strandlike markings in the lungs (fig. 2 *B*).

CASE 7.—The patient was a 26 year old Negro, whose complaints were fever, pains in the chest and cough. He had questionable enlargement of the cervical lymph nodes and bilateral iridocyclitis. The tuberculin patch test gave a negative reaction. He ran a febrile course throughout, the temperature reaching as high as 105 F. While he was under observation, small cutaneous nodules developed in the right leg and left forearm. Biopsy of these nodules showed changes consistent with the picture of sarcoid. There was some improvement in the eyes but no improvement in general condition, and he was transferred to a Veterans' Facility hospital for further treatment. This patient showed two features of interest. He had a decided elevation of temperature during his entire three months of observation. The second point is the fact that the cutaneous nodules were not obvious and were only found on search for a source of material for biopsy.

CASE 9.—A 21 year old white man was injured in combat by a shell fragment, resulting in the loss of one leg and a compound fracture of the other.

On his evacuation to this hospital a roentgenogram of the chest was taken because of a chronic persistent cough. An enlargement of the paratracheal and peribronchial lymph nodes bilaterally was revealed (fig. 6 *A*). The nodes were smooth and rounded and did not tend to be confluent. No calcifications were seen, and no compression of the trachea or bronchi was apparent. The patient stated that he had had a persistent cough of about two months' duration prior to this time. All laboratory studies were noncontributory except that on one occasion there was an eosinophil content of 11 per cent (table 2).

A small lymph node removed from the cervical chain showed most of the parenchyma replaced by rather sharply demarcated tubercles composed of epithelioid cells and occasional large multinucleated giant cells. There was necrosis in the center of some of the tubercles, but no actual caseation was encountered. Ziehl-Neelsen stain showed no acid-fast bacilli.

Over a period of nine months a gradual regression in the size of the mediastinal lymphadenopathy was noted, but simultaneously there appeared a faint strandlike

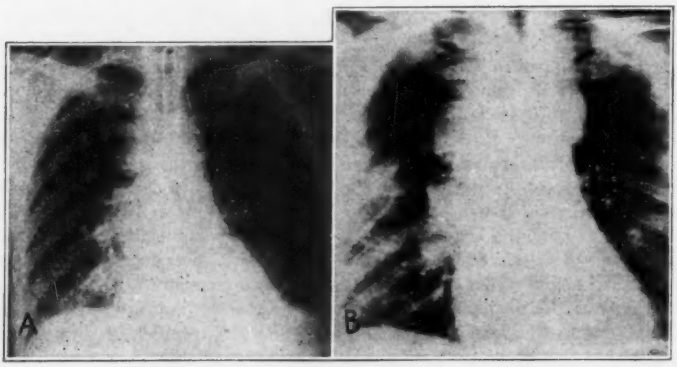

Fig. 10 (case 17).—*A*, on July 10, 1943, there is moderate enlargement of the peribronchial lymph nodes. The esophagus can be seen outlined by a small amount of barium. Just below the carina it shows considerable deviation, which is probably due to the enlargement of the bifurcation group of lymph nodes. *B*, on Feb. 1, 1946 the patient had a thoracotomy performed, and a lymph node was removed from the anterior mediastinum, which on final examination disclosed sarcoid. There has been a further enlargement of lymph nodes in the paratracheal region.

infiltration throughout both pulmonary fields (fig. 6 *B*). During the period of observation, the patient remained in comparatively good health and had only a slight occasional cough.

CASE 10.—The patient was a 31 year old white man who while being treated in the dispensary for pain in his left knee in March 1943 complained of dyspnea on strenuous exertion. He was then noted to have generalized lymphadenopathy of the sublingual, cervical, left epitrochlear and inguinal nodes. Biopsy of a sublingual node on April 7 showed the typical pathologic appearance of sarcoid.

Later, low grade fever developed and the liver became palpable, and by May 2 he had orthopnea and a pericardial friction rub was heard. On May 3 the pulse was weak and rapid (100 to 120) and the small volume and pulsus paradoxus were

confirmed by blood pressure readings. On May 5, 200 cc. of straw-colored fluid was removed from the pericardial cavity, with some relief of dyspnea (fig. 7). The blood pressure was 100 systolic and 70 diastolic before and 110 systolic and 70 diastolic after the aspiration.

There were 11,000 to 14,000 leukocytes, with a normal differential count. The temperature varied from 99 to 101 F., and the sedimentation rate was 57 mm. in one hour (Wintrobe).

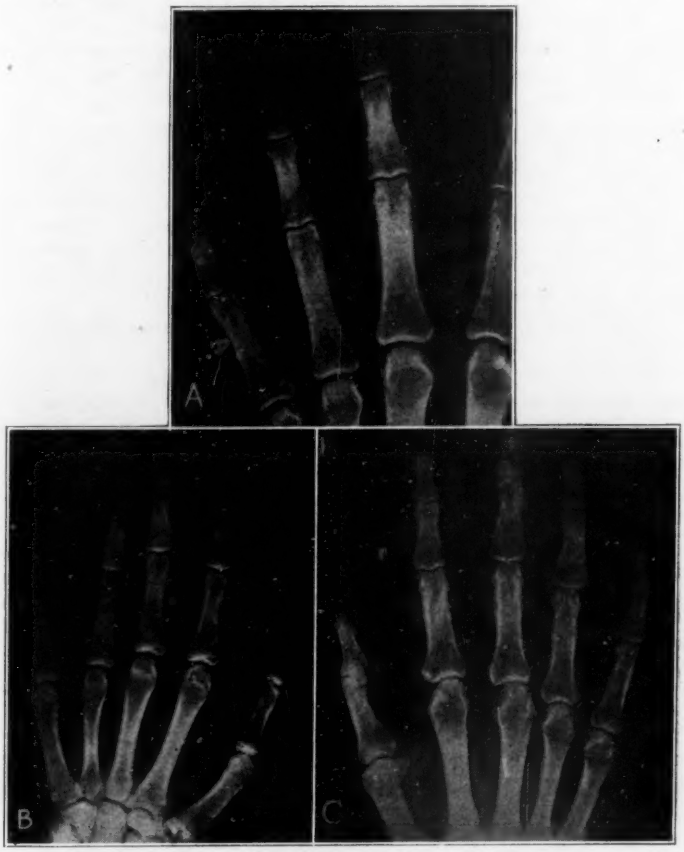

Fig. 11.—*A* (case 1), small oval areas of diminished density are noted in the distal and proximal ends of the phalanges. *B* (case 3), there is a diffuse rarefaction of the bones, with the areas of diminished density localized predominantly along the ends of the phalanges. No disturbance of epiphysial growth was noted in the hands of this adolescent patient during the period of observation. *C* (case 17), a diffuse rarefaction of the bones is seen in the hands of this patient, with occasional small oval areas of diminished density.

The patient received roentgen therapy, 1,300 r. at 220 kilovolts directed to the mediastinum, without noticeable effect. A total of 1,200 cc. of fluid was removed

from the pericardial cavity on three occasions. Repeated cultures on this fluid failed to reveal tubercle bacilli. He showed slow but steady improvement during the autumn and winter of 1943-1944 and became asymptomatic. He secured a medical discharge from the service in February 1944. The total period of observation was eleven months.

CASE 17.—The patient was a 58 year old white man who enjoyed good health until August 1943, at which time he was found to have a mediastinal tumor (fig. 10 *A*). The tumor appeared to be due to a cluster of enlarged lymph nodes about the trachea. A thoracotomy was performed at another hospital, and one of the nodes was removed for section. The initial impression of the pathologist was that the tumor was a tuberculoma, but there were some features that suggested a Hodgkin granuloma.

In May 1945 the patient complained of weakness and dyspnea on exertion, and laboratory studies disclosed anemia of the hemolytic type, with splenomegaly. There were also hyperglobulinemia and a positive reaction to a cephalin flocculation test (3 plus). It was believed that this was a case of latent congenital hemolytic anemia, and splenectomy was performed in May 1945. The postoperative course was uneventful; however, the blood picture was not significantly altered. The pathologic changes in the spleen were consistent with the diagnosis of "hemolytic anemia," and no lesions of sarcoid were seen.

In January 1946 the patient again returned to this hospital, complaining of weakness and dyspnea. He had definite anemia, with 3,200,000 red cells and a 64 per cent hemoglobin content. There was a slight increase in fragility of the red cells. The total protein was 7.3 Gm. per hundred cubic centimeters, with albumin 4.0 Gm. and globulin 3.3 Gm. A review of the previous roentgenograms indicated that there had been an increase in the size of the lymph nodes in the paratracheal and peribronchial regions plus a strandlike infiltration in both pulmonary fields (fig. 10 *B*). The bones of the hands showed a generalized rarefaction, with several small oval areas of diminished density (fig. 11 *C*).

A review of the slides made from the lymph node removed from the anterior mediastinum two and one-half years previously showed the typical noncaseating tubercles of sarcoidosis. The anemia in this patient was not thought to be due to replacement of the bone marrow but to the formation of autohemolysins. Any relation which this formation of autohemolysin may have to sarcoidosis is conjectural.

SUMMARY

1. Of 28 proved cases of sarcoidosis, the majority of the patients were found to be young adults; 27 were men, and 15 were Negroes. This distribution is somewhat influenced by the fact that the patients were drawn from young male military personnel.

2. The symptomatology is reviewed. It is apparent that the vast majority of cases of sarcoidosis fall into four major clinical groups: (*a*) dermatologic involvement, (*b*) uveoparotid fever, (*c*) generalized lymphadenopathy and (*d*) pulmonary infiltration.

3. We were not able to confirm the incidence of leukopenia observed by other authors. Anemia was found in only 2 cases. Eosinophilia was infrequent, and the monocytes were not consistently increased.

4. No instance of a false positive reaction to a serologic test for syphilis was noted.

5. The finding of a frequently negative reaction to the tuberculin test and of a high globulin value was confirmed.

6. A detailed roentgen study of the 28 cases revealed the following features: (*a*) enlargement of the paratracheal lymph nodes in all; (*b*) enlargement of the peribronchial lymph nodes in 25; (*c*) pulmonary parenchymal involvement in 15; (*d*) pleural effusion in 2 instances; (*e*) pericardial effusion in 1 instance, and (*f*) osseous changes in the hands of 6 patients.

7. In 11 of the 28 cases the enlargement of the intrathoracic lymph nodes was more prominent on the right side, which may be explained on the basis of the anatomic finding that in the normal chest the lymph nodes are more numerous on this side. This fact is of no value in the differential diagnosis of benign and malignant lymphogranuloma, as was once suspected.

8. In 27 of the 28 cases the enlarged intrathoracic lymph nodes tended to remain discrete and well defined. Calcification within the lymph nodes was seen in only 1 instance.

9. In the course of the disease the enlarged lymph nodes may undergo spontaneous regression, to be replaced by fibrous tissue; this may be accompanied with increased evidence of parenchymal pulmonary involvement.

10. There was but 1 death in this series, which was due to failure of the right side of the heart secondary to extensive infiltration of the pulmonary involvement.

11. Radiation therapy was of no value in the treatment of the enlarged lymph nodes of sarcoidosis in the 2 cases in which it was tried.

PENICILLIN IN CARDIOVASCULAR SYPHILIS

Early Reactions to Administration

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AND
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A FULL evaluation of the results of penicillin therapy in cardiovascular syphilis will require observations on treated patients over a period of many years. At present, it is possible to analyze only the early reactions to administration of penicillin.

In early syphilis [1] and in neurosyphilis [2] the Jarisch-Herxheimer reaction ("therapeutic shock") is a frequent immediate effect of penicillin therapy. This phenomenon is of potential importance in cardiovascular syphilis because of the theoretic possibility of the occlusion of the coronary orifices or of the rupture of an aneurysm.

Moore [1a] has advised that in the treatment of cardiovascular syphilis with penicillin "extreme caution should be exercised to avoid therapeutic shock within the first few days of treatment." This warning is based on 4 cases reported in the literature. Dolkhart and Schwemlein [3]

Read in abstract at the symposium, Recent Advances in the Investigation of Venereal Diseases, held on April 17, 1947, in Washington, D. C., under the auspices of the Syphilis Study Section of the National Institute of Health.

This work was performed under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Johns Hopkins University School of Medicine and United States Public Health Service Venereal Disease Research and Post-Graduate Training Center and under a grant-in-aid from the Research Grants Office, National Institute of Health, United States Public Health Service.

1. (*a*) Moore, J. E.: Penicillin in Syphilis, Springfield, Ill., Charles C Thomas, Publisher, 1947, pp. 55-56. (*b*) Farmer, T. W.: The Jarisch-Herxheimer Reaction in Early Syphilis, to be published.

2. (*a*) Reynolds, F. W.; Mohr, C. F., and Moore, J. E.: Penicillin in the Treatment of Neurosyphilis: II. Dementia Paralytica, J. A. M. A. **131**:1255 (Aug. 17) 1946. (*b*) Tucker, H. A., and Robinson, R. C. V.: Neuropsyhilitic Patients Treated with Penicillin: Probable Herxheimer Reactions, ibid. **132**:281 (Oct. 5) 1946. (*c*) Stokes, J. H.; Steiger, H. P.; Gammon, G. D.; LaMotte, W. O.; Beerman, H.; Ingraham, N. R.; Gyorgy, P.; Rose, E. K., and Lentz, J. W.: Three Years of Penicillin Alone in Neurosyphilis, to be published.

3. Dolkhart, R. E., and Schwemlein, G. X.: The Treatment of Cardiovascular Syphilis with Penicillin, J. A. M. A. **129**:515 (Oct. 13) 1945.

described 2 cases in which injection of penicillin was discontinued because of severe angina, which they attributed to the drug. Callaway and his co-workers [4] reported the probable rupture of an aortic cusp in 1 of their patients several weeks after penicillin therapy had been completed, and they attributed this to therapeutic shock. Moore [1] has reported a case of syphilitic aortitis in which the patient died in cardiac failure on the fourth day of combined malaria and penicillin therapy. The observations at necropsy in this case suggested to him the possibility of therapeutic shock. However, the evidence presented in these reports in favor of regarding any of the 4 cases as examples of Herxheimer reactions in cardiovascular syphilis is flimsy. Other investigators [5] have not encountered serious reactions during administration of penicillin in a total of 16 patients with cardiovascular syphilis.

It is important to determine whether special precautions are indicated in this situation, not only from the standpoint of treatment of patients with recognized syphilitic cardiovascular disease but also because patients with cardiovascular syphilis are frequently given penicillin for other conditions, such as concomitant neurosyphilis, benign late syphilis or intercurrent acute infectious disease.

We have attempted to clarify this problem by presenting a preliminary estimation of the incidence and severity of untoward reactions occurring during the administration of penicillin to patients with cardiovascular syphilis.

SELECTION OF CASE MATERIAL

Between 1943 and 1947, as a part of the evaluation of penicillin therapy in late syphilis, patients with all forms of proved or suspected syphilitic heart disease were admitted to the Johns Hopkins Hospital. Cases of suspected uncomplicated syphilitic aortitis, syphilitic myocarditis or syphilitic coronary ostial stenosis were excluded from the present report because of the difficulty of establishing definitely the accuracy of the diagnosis. The data on syphilitic patients with evidences of rheumatic, severe hypertensive or arteriosclerotic heart disease were likewise omitted because it was impossible to determine clinically the relative extent of the cardiovascular damage due to syphilis. A total of 14 patients fell in these two excluded categories; no untoward reactions to penicillin were observed in them.

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4. Callaway, J. L.; Noojin, R. O.; Flower, A. H., Jr.; Kuhn, B. H., and Riley, K. A.: Use of Penicillin in the Treatment of Syphilis of the Central Nervous System, Am. J. Syph., Gonor. & Ven. Dis. **30**:110, 1946.

5. Russek, H. I.; Cutler, J. C.; Fromer, S. A., and Zohman, B. L.: Treatment of Cardiovascular Syphilis with Penicillin, Ann. Int. Med. **25**:957, 1946. Hill, W. R.: Problems Arising in the Treatment of Syphilis with Penicillin. New England J. Med. **235**:919, 1946.

There remained 22 patients with aortic insufficiency and 8 with saccular thoracic aortic aneurysm. In these patients not only could we be relatively certain of the correctness of the etiologic diagnosis but also there were clinical and/or roentgenologic evidences of syphilitic cardiovascular disease which could be evaluated objectively. Each patient was observed clinically and followed with various laboratory studies throughout the period of administration of the antibiotic.

AORTIC INSUFFICIENCY

The 22 patients with aortic insufficiency ranged in age from 37 to 68 years. Nineteen were men. Thirteen were Negroes. In 15 instances a history compatible with early syphilis was obtained. Twenty-one patients had repeated positive reactions to serologic tests, and in 16, including the patient with a negative serologic reaction, the cerebrospinal fluid reacted positively to the complement fixation tests for syphilis.[6] The presence of aortic insufficiency was established in each patient by a definite aortic diastolic murmur and the usual peripheral signs.

At the time of administration of penicillin, 11 of the patients had cardiac symptoms. Five had dyspnea and anginal attacks of one to four years' duration, 2 had dyspnea at rest and 4 had mild exertional dyspnea for less than one year. Two were in cardiac decompensation. Eleven patients had a definite increase in the transverse diameter of the heart on roentgenologic examination. Ten of fifteen electrocardiograms made before treatment were abnormal; left axis deviation was the usual finding, but bundle branch block was noted in one and left ventricular "strain" in two records. Four patients had received metal chemotherapy after the onset of cardiac symptoms but in no instance more recently than three months prior to administration of penicillin.

Sodium penicillin in aqueous solution was given intramuscularly to 6 patients in initial doses of 500 to 3,000 Oxford units; these doses were subsequently increased gradually over a period of days until 30,000 to 100,000 units was given every three hours. Sixteen patients were placed on schedules of 25,000 to 100,000 Oxford units every three hours from the outset. Sixteen received commercial preparations of penicillin, and the others were given crystalline penicillin G; no differences were observed in the two groups. Total dosages varied from 2,000,000 to 15,000,000 Oxford units, and in no case was any other antisyphilitic drug employed.

Four of the 22 patients had elevations of temperature of from 100.0 (37.8 C.) to 102.4 F. (39.1 C.) within the first sixteen hours of treatment; all 4 received large initial doses of the antibiotic (table). All

6. The abnormally high incidence of neurosyphilis in this group was due to the fact that most of the patients were selected for admission to the ward primarily for the study of the treatment of this disease with penicillin.

these patients had symptomatic neurosyphilis with abnormalities of the cerebrospinal fluid. Two patients who had had angina at rest for over a year prior to their admission to the ward complained of typical attacks during and subsequent to administration of penicillin. One of these received a large and one a small initial dose of penicillin (table). In 10 patients on whom electrocardiograms were made before treatment from one to three tracings were taken at daily intervals after the start of therapy; in none did the records show significant change. Total and differential leukocyte counts and sedimentation rates were similarly unaffected. All patients completed therapy on schedule and without other reactions.

AORTIC ANEURYSM

The 8 patients with aortic aneurysms ranged in age from 40 to 72 years. Four were Negroes. Six were men. All had positive reactions

Early Reactions to Administration of Penicillin in Thirty Patients with Cardiovascular Syphilis

Type of Cardiovascular Syphilis	Initial Penicillin Dosage (Oxford Units)	Number of Patients Treated	Early Febrile Reactions, No. of Patients	Cardiac Symptoms During Therapy, No. of Patients	Treatment Interrupted
Aortic insufficiency	500 to 3,000	6	0	1	0
	25,000 to 100,000	16	4	1	0
Aortic aneurysm	500 to 2,000	3	1	0	0
	50,000 to 100,000	5	0	0	0
Total		30	5	2	0

to the serologic tests for syphilis, and in 4 the cerebrospinal fluid reacted positively to the complement fixation tests; in 1 the fluid was not examined. In each a pulsating mediastinal mass continuous with the aorta was demonstrated roentgenologically. In 2 the syphilitic origin of the aneurysm was later confirmed at autopsy. Five had cardiovascular symptoms, and 3 were in cardiac decompensation at the time of administration of penicillin. Six of seven electrocardiograms made before treatment were abnormal. One patient had received inadequate metal chemotherapy, which had been discontinued three months before his admission to the ward.

Commercial sodium penicillin in aqueous solution was given intramuscularly to 6 patients and crystalline penicillin G to the other 2. Three started with small initial doses (500 to 2,000 Oxford units), which were later increased. Four received injections of 50,000 Oxford units and the other of 100,000 units every three hours. Total dosages of penicillin ranged from 2,000,000 to 10,000,000 units.

In 1 patient who received an initial dose of 500 Oxford units there was an elevation of temperature to 100.0 F. (37.8 C.) shortly after the

start of treatment. This patient also had neurosyphilis. In none of the patients did new symptoms suggestive of a treatment reaction develop. Electrocardiograms taken on 4 of the patients during administration of penicillin revealed no change from previous records. All patients finished their penicillin schedules without incident.

COMMENT

Data on the small group of patients presented here are of limited statistical value. Undoubtedly many times this number of patients with cardiovascular syphilis have received penicillin, either as antisyphilitic therapy or as treatment for intercurrent infections. No certainly identified instances of disastrous results have appeared in the literature.

In our study 2 patients had anginal attacks at rest during treatment. Since attacks of comparable severity and frequency occurred both before and after the administration of penicillin, we do not feel that the symptoms should be interpreted as reactions to this antibiotic substance.

Only 5 of our patients had febrile reactions early in the course of injections, and each had symptomatic late neurosyphilis with notable abnormalities in the cerebrospinal fluid. The incidence of these reactions in our group of 20 patients with neurosyphilis was therefore approximately 25 per cent. In a previous study on neurosyphilis,[4] the over-all incidence of febrile reactions during administration of penicillin was about 25 per cent. It is reasonable to assume, therefore, that the febrile reactions observed in our patients may have been related to the neurosyphilitic process rather than to the cardiovascular one. Febrile reactions occurred in none of the 10 patients without concomitant neurosyphilis.

As shown in the accompanying table, our patients fell into two dissimilar groups as regards dosage schedules. No significant differences in severity or incidence of febrile reactions or cardiac symptoms occurred in the two groups. Whereas small, gradually increasing doses of penicillin have been recommended,[7] as has the institution of treatment with bismuth,[8] our data fail to indicate the need for either of these expedients. Although our findings suggest that it is probably safe to treat patients with late cardiovascular syphilis with average therapeutic dosages of penicillin, final conclusions should not be drawn until many times the number of cases presented here have been carefully studied.

SUMMARY

Twenty-two patients with syphilitic aortic insufficiency and 8 with thoracic aortic aneurysm were treated by the intramuscular route with

7. Moore.[1a] Stokes and others.[2c] Callaway and others.[4]

8. Olansky, S.: The Herxheimer Reactions of Relatively Small Doses of Penicillin, Ven. Dis. Inform. **28**:26, 1947.

sodium penicillin in aqueous solution in total dosages ranging from 2,000,000 to 15,000,000 Oxford units.

Five patients had fever (100.0 to 102.4 F.) within the first sixteen hours of treatment. Two patients with long-standing angina at rest had attacks of usual severity and frequency during and subsequent to administration of penicillin. In no instance was the treatment schedule interrupted. No significant differences in the incidence of febrile reactions or cardiovascular symptoms occurred in 9 patients receiving small initial doses (500 to 3,000 Oxford units) as compared with that in 21 patients given large initial doses (25,000 to 100,000 Oxford units) of penicillin.

Penicillin is frequently administered to patients with cardiovascular syphilis. The absence of reported severe reactions proved to be due to treatment with penicillin tends to confirm our impression that the dangers of severe untoward reactions may have been unduly emphasized. More work must be done with various dosages of penicillin in patients with cardiovascular syphilis, however, before final conclusions are justified.

NOTE.—Since this paper was submitted, 4 additional patients with cardiovascular syphilis (1 with aneurysm and 3 with aortic insufficiency) were treated with initial doses of 50,000 to 100,000 Oxford units of crystalline penicillin G. Neither febrile Herxheimer reactions nor untoward symptoms referable to the cardiovascular apparatus were noted.

RHEUMATIC PNEUMONITIS

A Case of Widespread Chronic (Proliferative) Type with Acute (Exudative) Foci

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CERTAIN pulmonary lesions occurring in some cases during the course of rheumatic fever and designated as rheumatic pneumonitis [1] have been the source of much interest in recent years. That fleeting and migrating pulmonary involvement occurs in rheumatic fever has been known for some time. The historical aspects of this subject were presented by Paul.[2] Attempts to identify the lesions by study of the tissue as one of the protean inflammatory manifestations of the rheumatic state seem to have been made only within relatively recent years.

Rabinowitz [3] discussed the possibility that the fleeting pneumonopathy observed during rheumatic fever was due to the "rheumatic virus." Eiman and Gouley [4] described lesions in the lungs of 2 patients which they considered to be similar to rheumatic cardiac lesions. Naish [5] presented the pulmonary symptoms in 6 cases and expressed the view that the alterations observed were similar to the changes occurring elsewhere in the body during the course of rheumatic fever as described by Coombs.[6] Fraser [7] described "Aschoff nodules" in the lungs of patients with rheumatic fever.

Paul,[2] in reviewing this subject, concluded that insufficient evidence existed to support a strict specificity of the pulmonary lesions but

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1. They are also referred to as rheumatic pneumonia or pneumonopathy or the rheumatic lung.

2. Paul, J. R.: Pleural and Pulmonary Lesions of Rheumatic Fever, Medicine **7**:383-410, 1928.

3. Rabinowitz, M. A.: Rheumatic Pneumonia, J. A. M. A. **87**:142-144 (July 17) 1926.

4. Eiman, J., and Gouley, B. A.: Rheumatic Pneumonitis, Arch. Path. **5**:558-559 (March) 1928.

5. Naish, A. E.: The Rheumatic Lung, Lancet **2**:10, 1928.

6. Coombs, C. H.: The Microscopic or "Submiliary" Nodules of Active Rheumatic Carditis, J. Path. & Bact. **15**:489-499, 1911.

7. Fraser, A. D.: The Aschoff Nodule in Rheumatic Pneumonia, Lancet **1**: 70-72, 1930.

referred to the changes as fairly characteristic. Epstein and Greenspan [8] agreed with such conclusions and failed to observe Aschoff bodies in the lungs. Coburn [9] discussed the pulmonary consolidation of rheumatic fever as inflammatory in origin but without specific characteristics and masked by the attendant circulatory failure.

Tragerman [10] reported a case of rheumatic fever with a peculiar chronic productive type of pneumonitis. Cook,[11] however, found the histologic appearance of the lungs to present the picture of collapse and passive hyperemia rather than that of a specific inflammatory lesion. Howard,[12] on the other hand, reviewed the subject and gave additional emphasis to the specific nature of the pleural lesions.

Hadfield [13] agreed with Masson, Riopelle and Martin [14] and described characteristic alterations in the areas of gaseous exchange. Neubuerger, Geever and Rutledge [15] considered so-called Masson bodies to have a specific connotation in rheumatic pneumonitis. Herbut and Manges [16] presented strong evidence against such a view.

Gouley [17] emphasized the pathogenesis of the parenchymal pulmonary lesions of rheumatic fever, stressing particularly that passive hyperemia was not found to be a requisite for the development of the interstitial changes in the lungs.

Forbus [18] noted the temporary consolidation termed "rheumatic pneumonia," but he stated that he had not encountered a consolidation at

8. Epstein, E. Z., and Greenspan, E. B.: Rheumatic Pneumonia, Arch. Int. Med. **68**:1074-1094 (Dec.) 1941.

9. Coburn, A. F.: Relationship of the Rheumatic Process to the Development of Alterations in Tissues, Am. J. Dis. Child. **45**:933-972 (May) 1933.

10. Tragerman, L. J.: Rheumatic Pneumonia, Arch. Path. **22**:566-567 (Oct.) 1936.

11. Cook, S. T.: On The Association of Pulmonary Changes With Rheumatic Pericarditis, Brit. J. Child. Dis. **29**:264-267, 1932.

12. Howard, C. P.: The Rheumatic Lung, Ann. Int. Med. **7**:165-171, 1933.

13. Hadfield, G.: The Rheumatic Lung, Lancet **2**:710-712, 1938.

14. Masson, P.; Riopelle, J. L., and Martin, P.: Poumon rheumatismal, Ann. d'anat. path. **14**:359-382, 1937.

15. Neubuerger, K. T.; Geever, E. F., and Rutledge, E. K.: Rheumatic Pneumonia, Arch. Path. **37**:1-15 (Jan.) 1944. Neubuerger, K. T., and Geever, E. F.: Rheumatic Pneumonia, Rocky Mountain M. J. **41**:167-168, 1944.

16. Herbut, P. A., and Manges, W. E.: The "Masson Body" in Rheumatic Pneumonia, Am. J. Path. **21**:741-752, 1945.

17. Gouley, B. A.: (*a*) The Evolution of the Parenchymal Lung Lesion in Rheumatic Fever and Their Relationship to Mitral Stenosis and Passive Congestion, Am. J. M. Sc. **196**:1-10, 1938; (*b*) The Role of Mitral Stenosis and of Post-Rheumatic Pulmonary Fibrosis in the Evolution of Chronic Rheumatic Heart Disease, ibid. **196**:11-18, 1938.

18. Forbus, W. D.: Reaction to Injury, Baltimore, Williams & Wilkins Company, 1943.

autopsy that could be considered truly rheumatic in origin, even when acute myocarditis existed. The clinically observed phenomenon was, therefore, interpreted as the result of a mechanism "not peculiar to rheumatic fever."

More recently, Jensen [19] and Griffith, Phillips and Asher [20] have reported on rheumatic pneumonitis. Death in Jensen's case was analyzed as being primarily due to acute pulmonary lesions. Griffith and his associates described and classified the lesions in 119 instances of pulmonary involvement in 1,046 cases of rheumatic fever (an incidence of 11.3 per cent). They interpreted rheumatic pneumonitis as an entity "only when considered as one of the manifestations of the widespread angiitis of rheumatic fever."

Swift [21] has for some time laid emphasis on the allergic aspect of rheumatic fever. Melnick [22] discussed the findings at autopsies on 6 patients who died from acute rheumatic fever, and he concluded that the pulmonary "process resembles an allergic reaction." More recently, Gregory and Rich [23] have presented additional data in support of hypersensitivity in the development of the lesions of rheumatic fever. The pulmonary lesions were included in the mechanism, and great stress was given to vascular alterations. Von Glahn and Pappenheimer [24] earlier reported on lesions in arteries during rheumatic fever and described the sequence of changes in the arterial wall. The pulmonary arteries were involved not infrequently in their group of cases. Paul [25] also discussed lesions of pulmonary arteries.

Such a review of this topic, although affording an insight into differences of opinion, nevertheless demonstrates that several observers have noted the development of fairly characteristic pulmonary changes in the

19. Jensen, C. R.: Nonsuppurative Poststreptococcic (Rheumatic) Pneumonitis: Pathologic Anatomy and Clinical Differentiation from Primary Atypical Pneumonia, Arch. Int. Med. **77**:237-253 (March) 1946.

20. Griffith, G. C.; Phillips, A. W., and Asher, C.: Pneumonitis Occurring in Rheumatic Fever, Am. J. M. Sc. **212**:22-30, 1946.

21. Swift, H. F.: Rheumatic Fever; Hektoen Lecture, Billings Foundation, J. A. M. A. **92**:2071-2083 (June 22) 1929.

22. Melnick, P. J.: Pulmonary Changes in Rheumatic Fever, Illinois M. J. **73**:336-340, 1938.

23. (*a*) Gregory, J. E., and Rich, A. R.: Experimental Production of Anaphylactic Pulmonary Lesions with Basic Characteristics of Rheumatic Pneumonitis, Bull. Johns Hopkins Hosp. **78**:1-12, 1946. (*b*) Rich, A. R.: The Role of Hypersensitivity in the Pathogenesis of Rheumatic Fever and Periarteritis Nodosa, Proc. Inst. Med. Chicago **15**:270-280, 1945.

24. Von Glahn, W. C., and Pappenheimer, A. M.: Specific Lesions of Peripheral Blood Vessels in Rheumatism, Am. J. Path. **2**:235-249, 1926.

25. Paul, J. R.: Lesions in the Pulmonary Artery in Rheumatism, Arch. Path. **3**:354 (Feb.) 1927.

course of rheumatic fever. Lack of unanimity has existed, particularly regarding the specificity of the lesions. The theory that the lesions develop independently of the changes ascribed to passive hyperemia in textbooks on pathology [26] appears to have received considerable support.

The as yet controversial aspects of this subject make the case herein presented of interest, since the diffuse changes in the lungs were clearcut and associated with a classic rheumatic type of carditis. Moreover, detailed descriptions of pulmonary lesions associated with rheumatic fever are readily available,[27] but the cases described as displaying active rheumatic carditis and extreme and diffuse interstitial pneumonitis with advanced fibrosis ("fibro-elastosis" of Gouley) and arterial lesions are few in number. Finally, our case offers an additional point of interest in that the pulmonary lesions resemble in several respects the changes described by Hammon and Rich,[28] that is, acute diffuse interstitial pulmonary fibrosis not necessarily associated with rheumatic cardiac lesions.

REPORT OF A CASE

SYNOPSIS OF CLINICAL RECORD.—A 25 year old white woman was admitted to Baylor Hospital on five separate occasions during a period of sixteen months. Clinically the case was considered to be one of classic mitral stenosis with repeated bouts of congestive failure. The past history divulged an attack of "flu" at the age of 13 years, which was said to have "settled in her heart." Blindness had existed since an "eye infection" shortly after birth.

On each admission to the hospital the patient's main complaints included dyspnea, orthopnea, cough (at times productive of tenacious sputum), palpitation and on one occasion substernal pain. On the second, third and fourth admissions, in addition to congestive failure, there were bouts of fever (temperature usually 100 F. and at times 99 to 105 F. by mouth), with leukocytosis (white blood cell count 22,000, with 86 per cent polymorphonuclear cells). The febrile state was controlled with penicillin therapy (30,000 units every three hours for five to fifteen days). Digitalis preparations were used for the cardiac failure.

The laboratory findings throughout the entire time can be summarized as follows: The white blood cell count was 18,000 to 22,000, with 86 per cent neutrophils, during the febrile periods and 5,000 to 9,800, with 73 to 78 per cent neutrophils, during the afebrile intervals. The red blood cell count was 3,700,000 to 4,000,000, with a hemoglobin concentration of 8.9 to 10.4 Gm. per hundred cubic centimeters. Urinalyses showed a specific gravity of 1.008 to 1.024, an albumin content of from normal to 250 mg. per hundred cubic centimeters, few to many white blood cells and none to many red blood cells. Four blood cultures yielded no growth. The Kahn, Kline and Wassermann serologic tests

26. Karsner, H.: Human Pathology, ed. 6, Philadelphia, J. B. Lippincott Company, 1942. Boyd, W.: The Pathology of Internal Diseases, ed. 3, Philadelphia, Lea & Febiger, 1940.

27. Naish.[5] Epstein.[8] Hadfield.[13] Gouley.[17a]

28. Hammon, L., and Rich, A. R.: Acute Diffuse Interstitial Fibrosis of the Lungs, Bull. Johns Hopkins Hosp. **74**:177-212, 1944.

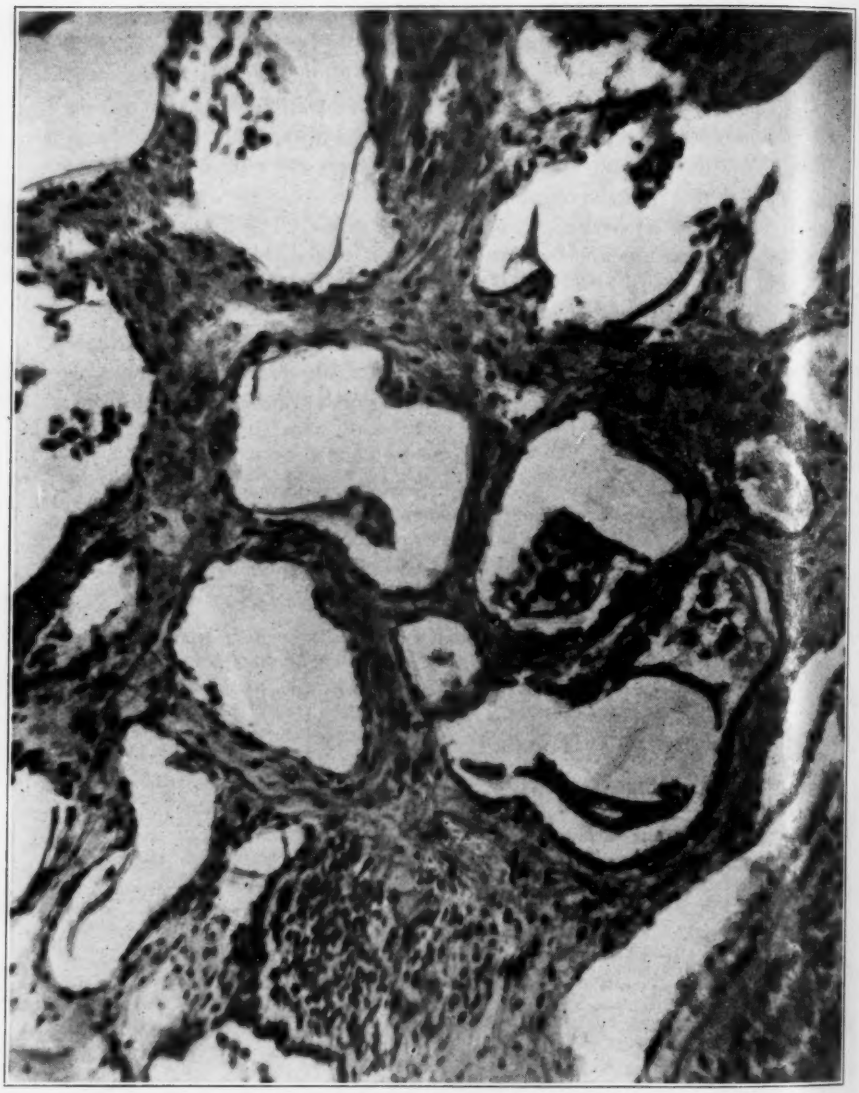

Fig. 1.—Section of the lower lobe area demonstrating remnants of hyaline membranes and hemosiderin-containing macrophages in alveolar spaces. The alveolar walls are fibrously thickened and show a decrease in vascularity and scattered groups of inflammatory cells, mainly lymphoid cells and macrophages. The cuboidal lining of alveolar spaces is also pictured.

of the blood elicited negative reactions. No cold agglutinins were observed. Erythrocyte sedimentation rates (Cutler) were 22 to 26 mm. in one hour.

Roentgenograms of the chest revealed enlargement of the left auricle, deviation of the esophagus to the right and pulmonary congestion. After the patient's fourth admission to the hospital (May 28, 1946), a report on a roentgenogram described the presence of confluent pneumonic consolidation of the base of the right lung. The existence of "rheumatic pneumonitis" was considered at this time.

During the final stay in the hospital (June 27 to July 7, 1946), the outstanding features were remittent fever peaks of 101 F., backward heart failure and signs of consolidation in the middle and lower lobes of the right lung. A roentgenogram demonstrated patchy and confluent consolidation of the lower lobe of the same lung and bilateral pleural thickening. Cyanosis was not intense. The patient died nine days later after being in a shocklike state for a few hours.

AUTOPSY.[29]—*Gross Findings.*—The body was that of a poorly nourished white woman 59 inches (150 cm.) in length and with an approximate weight of 100 pounds (45 Kg.). The corneas were thickened and opaque. There was an old midline scar in the lower part of the abdomen (appendectomy scar). The skin was everywhere pale.

The right pleural space had 800 cc. of dark brown fluid and the left pleural space 300 cc. There were no pleural adhesions. The pericardial space had 100 cc. of yellowish fluid, and the pericardial surfaces were smooth and glistening.

Heart: The weight of the heart was 260 Gm. The left ventricle was small and the left antrum large and dilated. The right atrium and right ventricle were moderately enlarged. The myocardium was firm and reddish brown. The circumference of the valves in centimeters was as follows: tricuspid 10, pulmonic 6, mitral 2 and aortic 7. The mitral leaflets were adherent and thickened and formed a fixed, markedly stenosed, funnel-shaped structure; the chordae tendineae were shortened and thickened. At the near edge of the fused leaflets were minute, friable, verrucous vegetations. There was a single vegetation 3 mm. in diameter on the posterior atrial wall, 1 cm. above the posterior mitral leaflet (MacCallum patch area). The other valves were unaltered, and the remainder of the endocardium was smooth. The coronary vessels were of normal appearance.

Lungs: The weight of the right lung was 1,000 Gm. and that of the left 800 Gm.

The pleura of the right lung was thickened, especially over the lower lobe. All three lobes were firm and retained their shape well. The only area of normal crepitation was an area 5 cm. in diameter about the apex. On section the upper lobe was firm and dark red, and abundant frothy fluid could be expressed from the cut surface. The upper half of the lower lobe was of the same appearance as this. The entire middle lobe and the lower half of the lower lobe were firm and rubbery and yellowish gray, with a dry cut surface from which little air escaped.

The left lung resembled its fellow. The entire upper lobe was dark red and firm and exuded frothy fluid on section. The entire lower lobe was pale gray, firm, rubbery and dry and resembled the lower area of the right lung.

The bronchi on both sides were nearly empty and showed no dilatation. The larger blood vessels were grossly unaltered. There was no evidence of tuberculous lesions at the apex.

29. Autopsy was performed three hours after death.

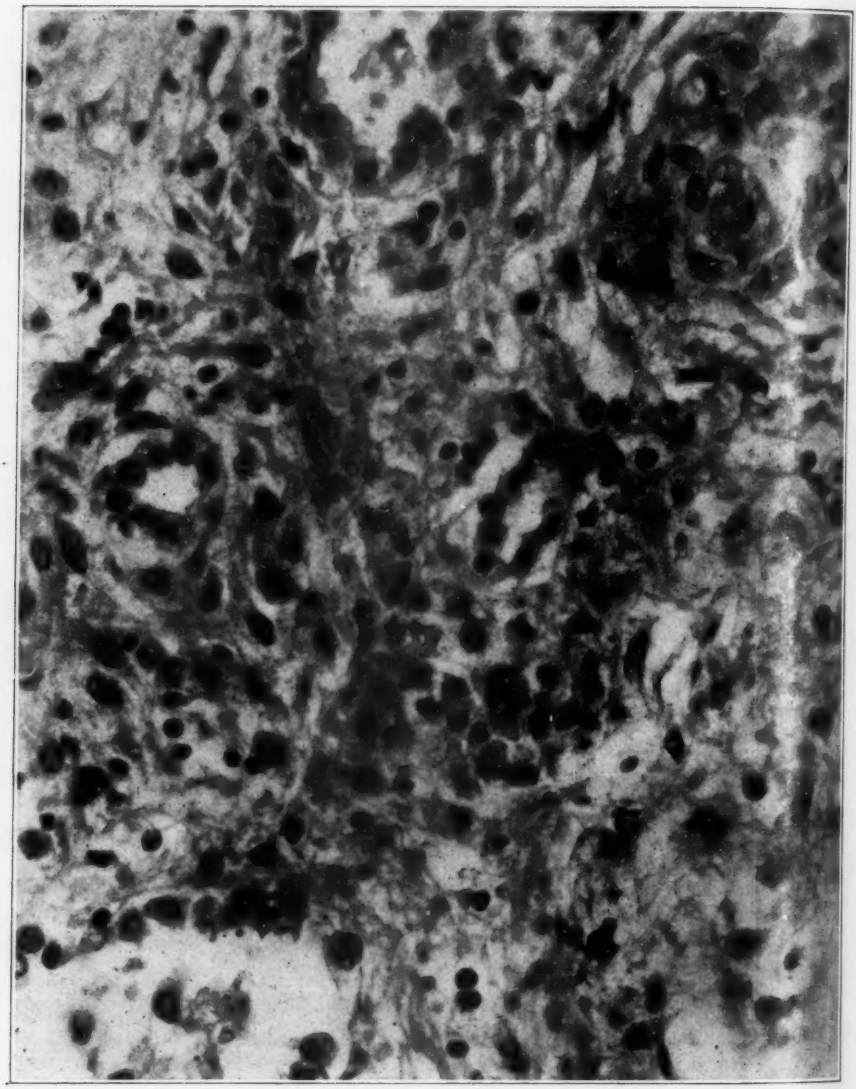

Fig. 2.—A closer observation of the thickened alveolar walls. Fibroblasts and intercellular fibers containing the mononuclear exudate are seen. Again the disturbed vascularity and the cuboidal lining of alveolar spaces can be noted.

Liver: The weight was 1,330 Gm., and section showed the dark red and gray mottling of passive hyperemia.

Spleen: The spleen weighed 190 Gm. and was firm and rubbery.

Kidneys: The weight of the right kidney was 140 Gm. and that of the left 150 Gm. The appearance was normal.

Other Organs: No gross abnormalities were noted in the esophagus, stomach, gallbladder, pancreas, adrenal glands, ureters, urinary bladder, uterus, uterine tubes, ovaries and central nervous system.

Microscopic Examination.[30]—Heart: Left ventricle. Prominent venocapillary hyperemia was present, with myocardial fibers of normal size. The myocardium near the epicardium was heavy with mononuclear cells (lymphoid and larger forms). There were similar cells in the connective tissue near the arterial branches plus occasional plasma cells, eosinophils and Aschoff cells (with lobulated vesicular nuclei, abundant purplish cytoplasm and ill defined borders). Some cellular accumulations were sufficiently concentrated to warrant the designation of Aschoff bodies.

Anterior mitral leaflet and aortic cusp. The mitral leaflet was thick and hyaline, and the aortic cusp was normal. Between these structures the myocardium had many dilated vessels and scattered small recent hemorrhages. The mural endocardium had many small mononuclear cells here.

Leaflet vegetation. Eosinophilic fibrin-like material with many polymorphonuclear neutrophilic leukocytes was present; the leaflet was partly calcified.

Left atrium at MacCallum patch. The connective tissue of the thickened endocardium had separated bluish granular collagen bundles. The adjoining connective tissue and the myocardium contained numerous oval and round cells of typical Anitschkow myocite type (nuclei with central chromatin condensation and strands radiating to nuclear membrane, ill defined cytoplasm and palisade-like arrangement).

Right side. There was no significant finding here.

Lungs: Upper lobes. The pleura was of normal thickness. The parenchymal alveolar pattern was regular, but the alveolar walls were greatly thickened because of considerable capillary hyperemia and increased cellularity. The cells consisted mainly of fibroblasts, but scattered lymphoid cells, plasma cells and macrophages were also seen. The lining of many alveoli was of the cuboidal epithelium type. The smooth muscle of the terminal bronchioles was hypertrophied.

The alveolar spaces were nearly empty in some areas but were filled with protein precipitate (edema) and hemosiderin-laden macrophages in others. Occasional hemosiderin-containing giant cells were seen. Ill defined to definite hyaline membranes were seen adhering to the lining of several alveolar ducts and alveoli.

Focal areas, involving 50 to 75 per cent of microscopic fields (60 diameters magnification), demonstrated replacement of alveolar pattern by a delicate and loose connective tissue. Such areas contained young plump type fibroblasts, fine, delicate intercellular fibrils, scattered lymphocytes, plasma cells and macrophages with and without hemosiderin pigment.

Groups of intact red blood cells were seen in some alveolar spaces (capillary hemorrhages); compact hemorrhages were not present. Larger blood vessels were distended with blood, but the walls were normal in appearance.

Lower lobes. The pleura was moderately thickened, containing fairly dense fibrous tissue, scattered capillary-sized blood vessels, prominent focal accumu-

30. The stain used was hematoxylin and eosin.

lations of inflammatory cells, mainly lymphocytes and macrophages, and a few eosinophils and plasma cells.

In the parenchyma the alveolar walls were greatly thickened and the alveolar spaces were small and lined with cuboidal epithelium. The thickening of the walls was due to abundant connective tissue having plump fibroblasts and loosely to

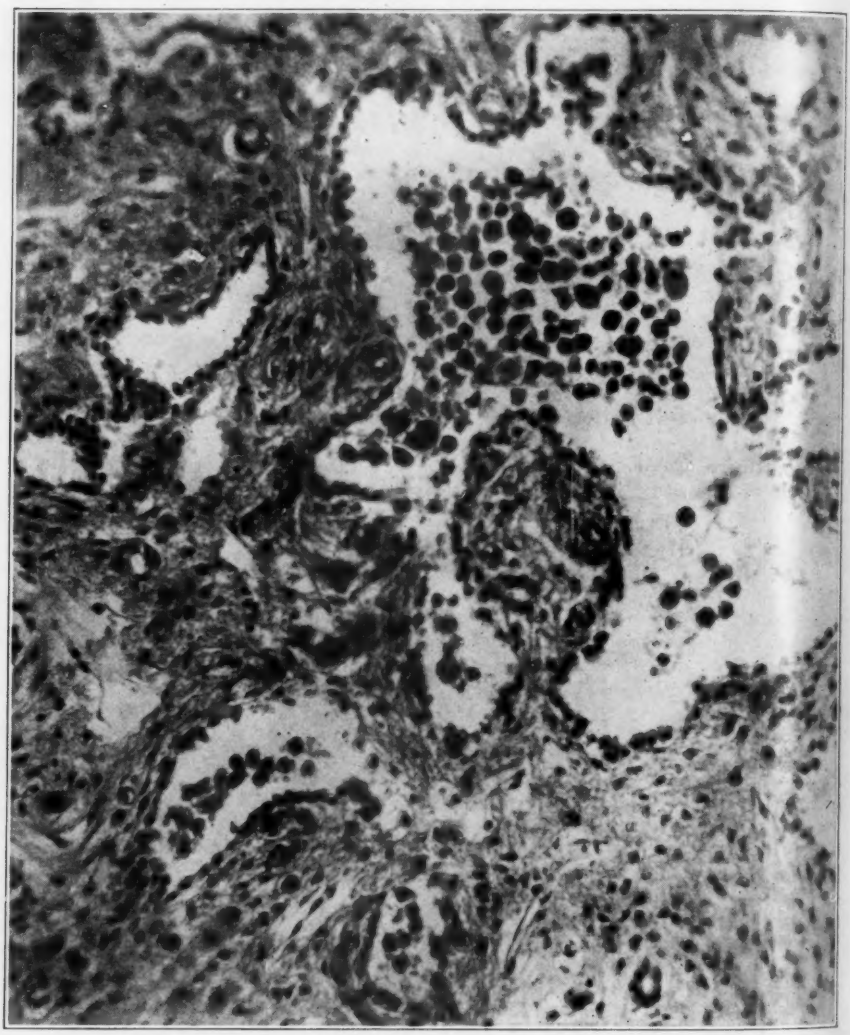

Fig. 3.—A so-called Masson body is demonstrated, being attached by means of a fibrous pedicle. The construction of these bodies is similar to that of the thickened alveolar walls. The intra-alveolar and interstitial cellular exudates can be noted to be similar.

densely arranged and intertwined intercellular fibers. There was pronounced infiltration of fibrous tissue with mononuclear cells (lymphocytes, plasma cells and macrophages). Hemosiderin-laden macrophages were present.

The number of capillaries in the alveolar walls was markedly decreased. The larger blood vessels were the seat of notable changes There was separation of the muscle bundles of the media by loose vascular connective tissue, and the lumens were replaced by connective tissue having scattered small blood vessels

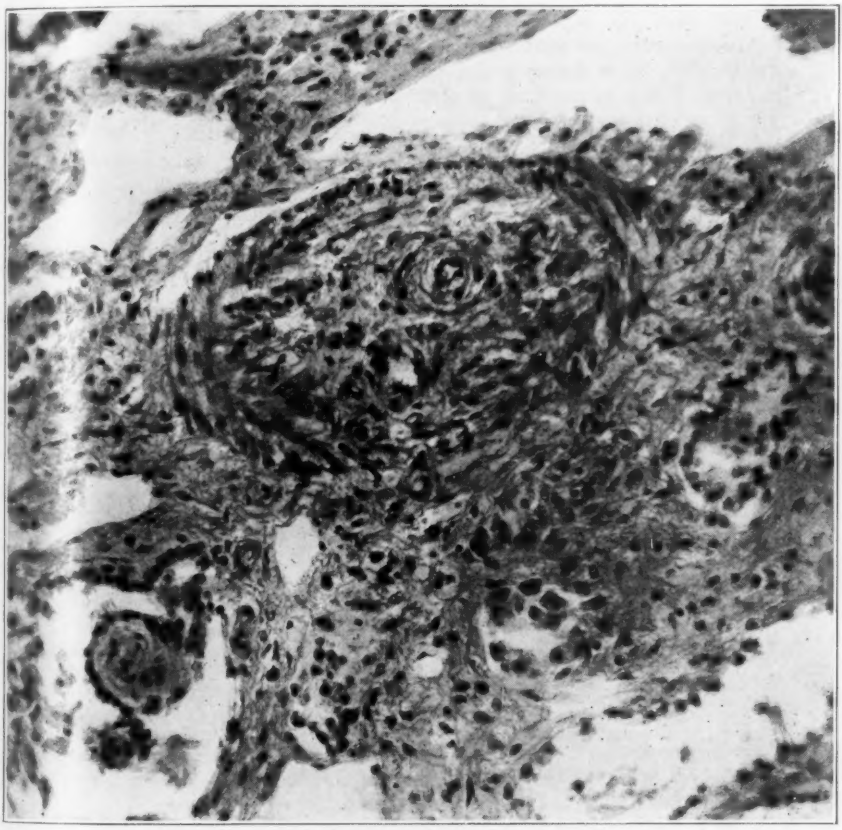

Fig. 4.—A close-up example of the healed arterial lesion is displayed. The resemblance to a canalized thrombus can be appreciated. Some portions of the muscular structure of the media have been separated by the loose type of connective tissue, while other portions remain intact. Another "Masson body" is noted in the left lower corner.

(appearance of canalized thrombi). In the loose connective tissue of the adventitia groups of round cells were seen (lymphoid and plasma cells and macrophages but no eosinophils).

The alveolar spaces either were empty or contained clusters of hemosiderin-laden macrophages. So-called Masson bodies were prominent everywhere. These

consisted of round or oval intra-alveolar masses, frequently seen to be attached to an alveolar angle by a small pedicle. The pedicle and the mass consisted of fibrous tissue of two types, either dense and compact or loose and delicate. The bodies were covered by cuboidal epithelium and infiltrated by round cells, the same as in alveolar walls.

The bronchiolar epithelial lining was folded in compressed fashion, and columnar cells had elongated hyperchromatic nuclei. Occasional remnants of hyaline membrane were seen.

Mediastinal Lymph Node: Pronounced hyperemia and polymorphonuclear neutrophilic leukocytes, plasma cells and macrophages were present in the sinuses and medullary cords (subacute lymphadenitis).

Liver: There was evidence of centrolobular hyperemia and atrophy. There was an increase in the fibrous tissue of portal areas, and lymphocytes, plasma cells and macrophages were seen.

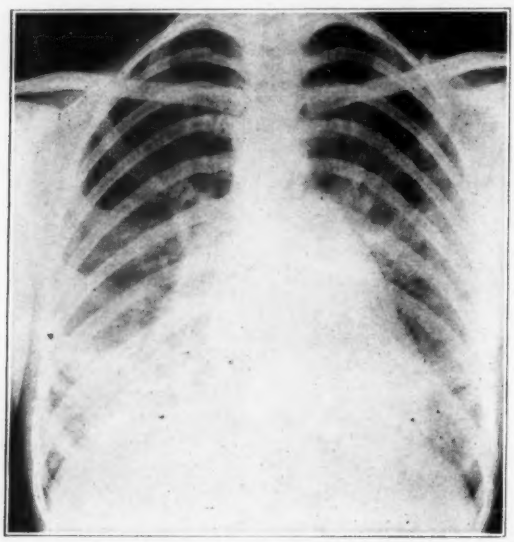

Fig. 5.—Roentgenogram taken fifty days before the patient's death shows pulmonary congestion and patchy and confluent pneumonic consolidation in the base of the right lung. The prominent left auricle and pulmonary conus are shown in the cardiac silhouette.

Spleen: Channelization of chronic passive hyperemia was seen in the spleen.

Kidneys: Protein precipitate was present in glomerular capsular spaces in the kidneys, with parenchymatous degeneration of convoluted tubules. There was calcification of many convoluted tubules (distal?) and collecting tubules in the cortex and medulla.

Other Organs: The adrenal glands, ureters, urinary bladder, uterus, uterine tubes, ovaries and central nervous system were of normal appearance.

Diagnosis.—The diagnosis was as follows: (1) rheumatic state with (*a*) advanced mitral stenosis, (*b*) verrucous endocarditis, mitral and atrial, (*c*) myocarditis of healed and active types and (*d*) pneumonopathy with extreme

diffuse fibrosis and partly healed arteritis; (2) chronic panvisceral passive hyperemia; (3) acute parenchymatous degeneration of the liver and kidneys; (4) focal calcification of the renal tubules, and (5) corneal opacities.

PULMONARY CHANGES IN RHEUMATIC PNEUMONITIS

Several observers have presented detailed description of the pulmonary changes in rheumatic pneumonitis. Despite some differences concerning specific aspects of the tissue response, a certain central theme can be appreciated in these various observations.

Gouley [17a] classified rheumatic pneumonopathy into acute, subacute and chronic forms. The acute form was considered to begin in a destructive phase (foci of fibrinoid necrosis in alveolar walls, monocytic infiltration and endothelial proliferation), which then passes into a proliferative phase (infiltration of large basophilic cells called "Aschoff cells" in perivascular and interstitial spaces), followed by a reparative phase (presence of plasma cells, lymphocytes and proliferated fibroblasts, with greater elaboration, and greater amounts of collagen and destruction of elastic and reticular framework of alveolar walls). In the subacute form the reparative process continues, giving rise to early diffuse interstitial fibrosis, many macrophages and early regeneration of elastic tissue ("elastosis"). The chronic form is characterized by thick alveolar walls due to collagenous fibrosis, diminished capillary blood supply, cuboidal alveolar lining and hyperplasia of elastic tissue ("elastosis"). Grossly, the early forms are featured by a mottled appearance resembling hemorrhagic edema, irregular infarcts or definite consolidation. The later forms give rise to varying degrees of "rubberoid" appearance of the lungs.

Epstein and Greenspan [8] described the pulmonary lesions in a related fashion. In patients who died during the initial attack of rheumatic fever the main microscopic changes included intra-alveolar and septal edema, capillary hyperemia and hemorrhages, the presence of large mononuclear cells, the formation of hyaline membranes in 50 per cent of the cases, early organization and fibrosis and occasional hyaline thrombi in arteries. Patients having had previous attacks of rheumatic fever demonstrated atelectasis, interstitial fibrosis, organization of alveolar exudate, large numbers of cells of the form found in heart failure, hypertrophy of respiratory bronchiole musculature, considerable intimal proliferation and narrowing of arteries and arterial thrombi.

Naish's [5] 6 patients had active rheumatic lesions elsewhere in the body. Grossly, the lungs displayed prominent areas of consolidation with "solid india rubber" appearance, being tough and red. Microscopically, the changes were considered similar to those described by Coombs and included proliferation of the endothelium of the smaller

blood vessels, fibroblastic proliferation about the capillaries, the presence of macrophages and sometimes hemorrhage.

Fraser [7] described exudative and proliferative features not unlike those just described but reported that typical Aschoff nodules were observed in 2 cases.

Hadfield [18] noticed the early presence of capillary hyperemia and fibrinous exudate in alveoli and alveolar ducts and emphasized the hyaline membrane. Later (after fourteen to twenty-one days) fibrosis and mononuclear infiltration became prominent. Farber and Wilson [31] demonstrated that two main factors were operative in the production of hyaline membranes, that is, the presence of fluid matter in the air passages and notable dyspnea.

Griffith, Phillips and Asher [20] considered the microscopic changes to be those of anaphylactic angiitis involving larger vessels and capillaries. They mentioned the following changes: endothelial proliferation, hemorrhage, necrosis, hyalinization and perivascular infiltration of plasmocytes, giant cells, lymphocytes and "myocytes with owl-eyed nuclei" and a few neutrophils. Aschoff bodies were found freely in various stages of development and maturity.

The findings in our case are similar to those described by Tragerman.[10]

Von Glahn and Pappenheimer [24] described arterial lesions in detail. In 47 cases of rheumatic heart disease they encountered involvement of pulmonary arteries in 21.2 per cent. Usually isolated segments of vessels were involved. The early phases were described as consisting of the following changes: swollen endothelium, accumulation of fibrinous exudate in the intima and in the entire wall, necrosis of the wall, occasional small hemorrhages, a peculiar loose cellular tissue beyond the necrotic wall having fibrillar stroma and many distorted nuclei and farther out young connective tissue with many capillaries and lymphoid cells, plasma cells and occasional eosinophils. The reparative phase was characterized by proliferation of endothelial cells and invasion by granulation tissue. The inflammatory cells disappeared, and the healed stage resembled canalized thrombi.

COMMENT

Another case in which healed and active rheumatic cardiac lesions and a unique diffuse pneumonitis and arteritis were demonstrated has been presented. The pulmonary lesions conform with those described by several observers during the course of the rheumatic state and considered by them as rheumatic pneumonitis. The repeated demonstration of the association of known rheumatic cardiac lesions and such peculiar

31. Farber, S. and Wilson, J. L.: The Hyaline Membrane in the Lungs: Experimental Study, Arch. Path. **14**:450-460 (Oct.) 1932.

pulmonary changes is of help in establishing more firmly the rheumatic basis for such lesions. It is with the aim of pointing out this association again that the present case is reported.

By Gouley's criteria the rheumatic pneumonopathy in the case presented conforms mostly with the chronic phase. Some features (hemorrhages, proliferating fibroblasts, delicate young connective tissue, cellular exudate and hyaline membrane) in less involved areas of the upper lobes were more in keeping with the earlier phases described by Gouley. It can be considered that healed and active processes were concomitantly present, apparently extending from the lower to the upper areas of the lungs. Aschoff cells and bodies, such as are observed in the heart and as were seen within the myocardium in this case, were not encountered in the lungs.

Several factors make the diagnosis of rheumatic pneumonitis greatly dependent on definite lesions of rheumatic fever present elsewhere in the body, preferably the heart, in addition to the fairly characteristic pulmonary changes. These factors include the lack of a specific pulmonary response which can be labeled as rheumatic beyond any doubt and, naturally, the inability to demonstrate the cause within the lungs. Other conditions may initiate tissue responses within the lungs that simulate rheumatic pneumonitis. This feature became particularly apparent when we compared the microscopic appearance in our case with that in certain cases presented by Hammon and Rich [28] as instances of acute diffuse interstitial pulmonary fibrosis. In this connection it is of interest that Rich [23b] has made observations pointing toward a common factor, hypersensitivity, in several types of tissue responses heretofore considered separately.

Attempts to establish the incidence of rheumatic pneumonitis have been made, a good example being the figure 11.3 per cent presented by Griffith, Phillips and Asher.[20] The distinct impression is gained, however, from the review presented at the outset that the incidence of cases in which the widespread chronic (proliferative) phase is displayed is not known. One does not hesitate to consider that the figure must be low, simply on the basis of the number of such cases mentioned so far in the literature. Only through more information concerning the incidence of the widespread chronic ("rubberoid") type of disease can it be possible to gain some knowledge concerning the percentage of cases in which the acute (exudative) phase passes into the extensive chronic (proliferative) phase.

SUMMARY

A case is reported which presents the concomitant occurrence of known healed and active rheumatic cardiac lesions and a peculiar interstitial and intra-alveolar pneumonitis. The pneumonitis was widespread, demonstrating a healed (proliferative) phase with extensive fibrosis and

an active (exudative) phase. In addition, partly healed arterial lesions were observed within the lungs.

The repeated observation of rheumatic lesions in association with pneumonitis is considered significant and supports the term rheumatic pneumonitis.

A review of leading observations on this condition has been made.

NOTE.—Since this report was completed we have observed another interesting case belonging to this category. A 21 year old white man with a clearcut history of rheumatic fever and congestive failure died suddenly (pulmonary embolism). The observations at autopsy were interesting. There were cardiac lesions of rheumatic fever type (in the myocardial, pericardial and MacCallum patch areas, anterior mitral leaflet and aortic valve). There was no mitral stenosis. The right lung was one-fourth the normal size, whitish and fibrous, and the left lung was fibrous and emphysematous. The microscopic picture was as follows: diffuse fibrous thickening of alveolar walls, prominent scattering of round cells and large clusters of hemosiderin-laden macrophages. Frequent loose irregular scars in the parenchyma, containing lymphocytes, macrophages and hemosiderin pigment, were seen. No arterial lesions were noted. There were focal lesions in the liver, pancreas and adrenal glands.

In this case the rheumatic state was associated with a demonstrable widespread inflammation, most pronounced in the lungs and heart. The pneumonitis and pleuritis were widespread and of the type encountered in the first case. The absence of mitral stenosis supports strongly the interpretation early expressed by Gouley that the pulmonary changes are due to active inflammation and not necessarily to the secondary changes of passive hyperemia associated with mitral stenosis.

Dr. H. M. Winans, Chief of the Medical Service of Baylor Hospital, assisted in the preparation of this report; the clinical studies were conducted under the supervision of Dr. A. S. McGee and Dr. J. S. Bagwell.

CONTAGIOUSNESS OF COCCIDIOIDOMYCOSIS

An Experimental Study

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THIS study is directed toward a reconsideration of the issue regarding the contagiousness of coccidioidomycosis. With the high incidence of infection that occurred in large numbers of troops trained in such endemic areas as southern California, parts of Texas, Arizona and New Mexico and with subsequent demobilization, numerous soldiers harboring the fungus will return to all parts of the United States.

For an accurate evaluation of contagiousness, the causative agent must be known in its various phases and the portal of entry of the causative agent must be well understood.

CAUSATIVE AGENT AND PORTAL OF ENTRY

A. *Causative Agent (Coccidioides Immitis.)*.—The fungus responsible for the disease has two distinct phases in its development, as follows:

1. In the animal host it is found as a refractile thick-walled spherule (fig. 1) filled with spores. The spores may be liberated by rupture of the wall of the cyst (fig. 2), whereupon each spore may go on to develop into a spherule. This cycle is continuous in vivo or limited, depending on the progression of the disease.

2. In culture the fungus produces mycelial threads and spores (chlamydospores); the latter are cylindric (fig. 3) and thus differ from the spheres just described. Rarely, chlamydospores have been found in large cavities of the lungs of human beings, and occasionally spherules have been reported in culture.[1]

From the Laboratory of the Bruns General Hospital, Santa Fe, N. Mex.

1. Baker, E. E., and Mrak, E. M.: Spherule Formation in Culture by Coccidioides Immitis, Am. J. Trop. Med. **21**:589, 1941. Lack, A. R.: Spherule Formation and Endosporulation of Fungus Coccidioides in Vitro, Proc. Soc. Exper. Biol. & Med. **38**:907, 1938. MacNeal, W. J., and Taylor, R. M.: Spherule Formation in Vitro, J. M. Research **30**:261, 1914.

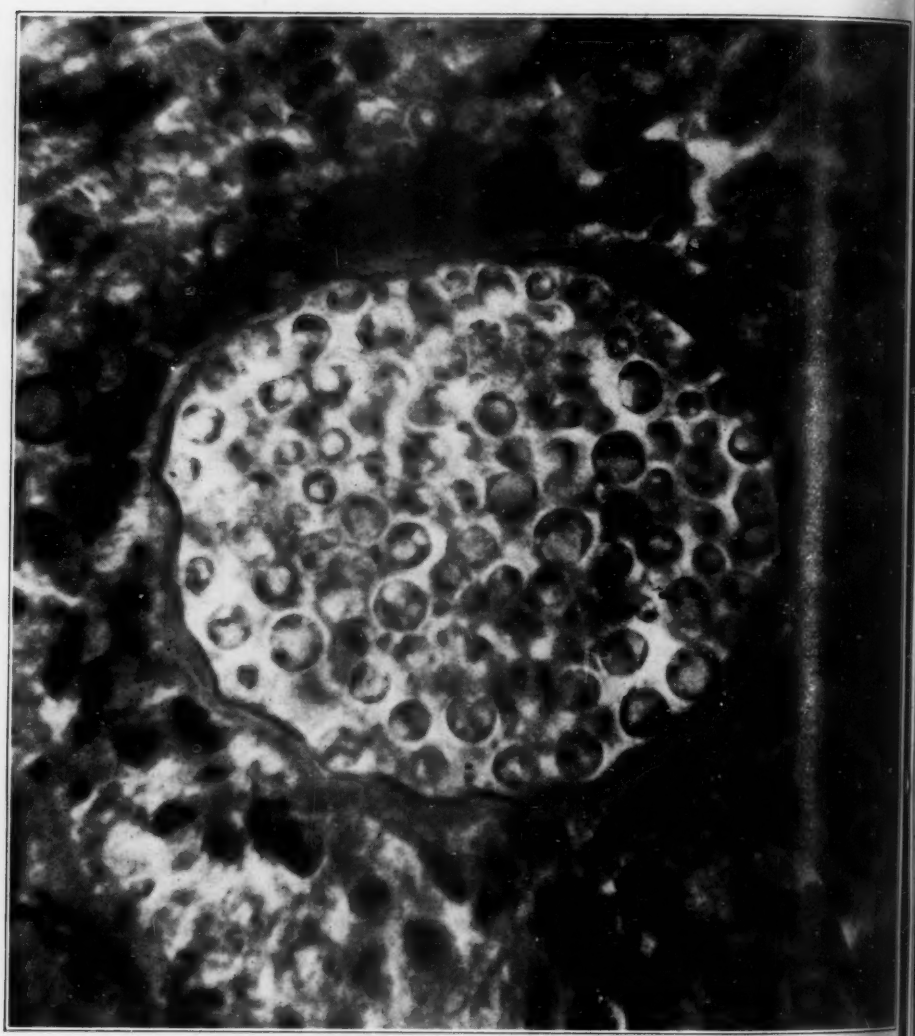

Fig. 1.—Thick-walled spherule (sporangium) filled with spherical spores. Verhoff-Van Gieson stain; × 786.

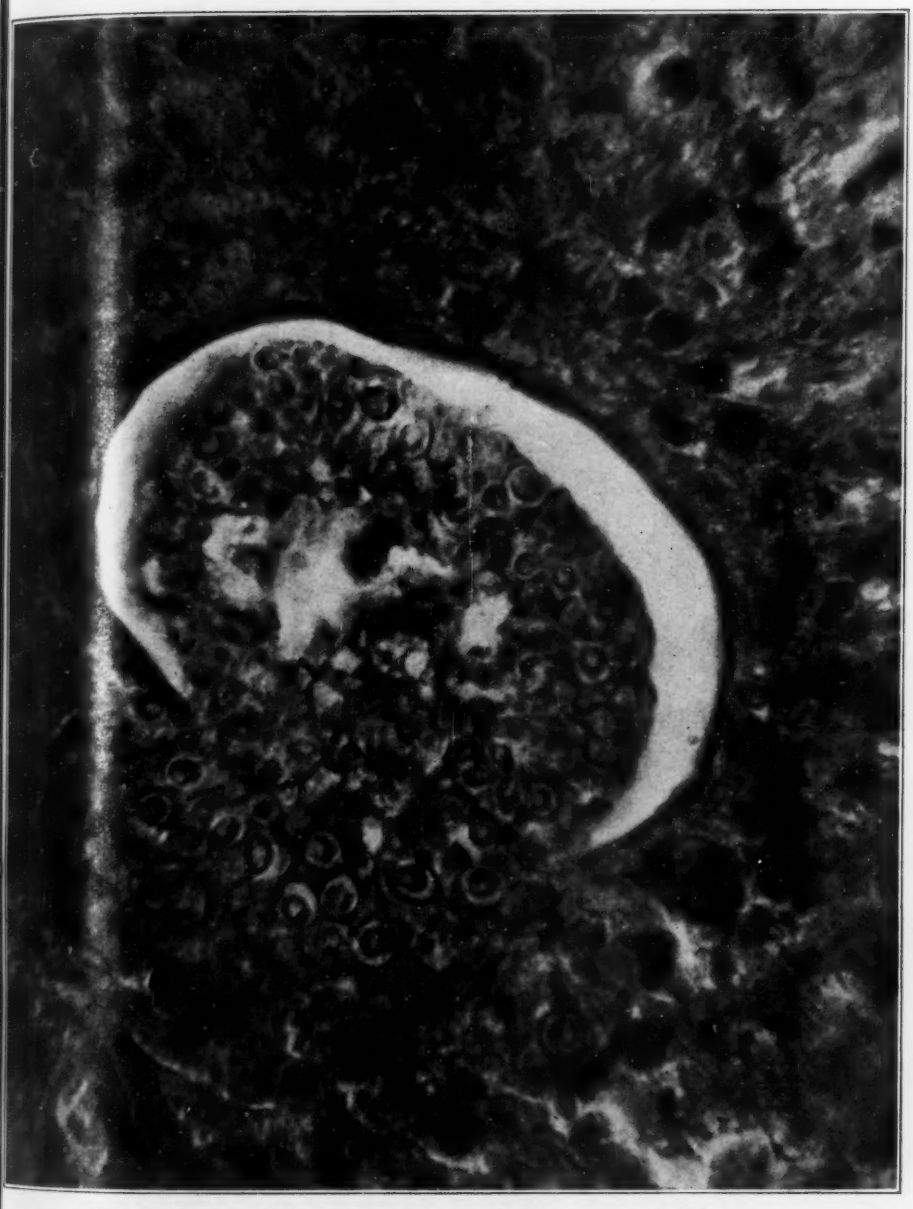

Fig. 2.—Rupture of spherule wall, with extrusion of spores. Verhoff-Van Gieson stain; × 758.

Steward and Meyer,[2] Smith and Baker[3] and Emmons[4] have isolated the organism in coccidioidomycosis from samples of soil. It is proposed that the disease in human beings is instigated by chlamydospores, although the latter were not demonstrated in the soil; the soil may not be the source of propagation of this fungus but simply the vehicle by which the disease is spread, i. e., dust. It is generally agreed that the spherules must undergo a stage of development in nature to form chlamydospores, as seen in culture, before becoming infectious to human beings. There appears to be unanimity of opinion that there is no evidence of transmission from person to person.[5]

B. *Portal of Entry.*—Since the work of Ophüls,[6] in 1905, it has been generally agreed that the usual portal of entry is the respiratory tract.[7] Kessel[7b] found that in 70 per cent of all cases observed at the Los Angeles General Hospital the disease originated in the lungs.

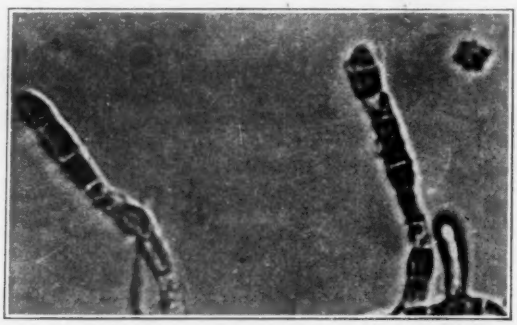

Fig. 3.—Chlamydospores in chains (ten day old culture). Note cylindric shape. Unstained; × 1,600.

2. Steward, R. A., and Meyer, K. F.: Isolation of Coccidioides Immitis from Soil, Proc. Soc. Exper. Biol. & Med. **29**:937, 1932.

3. Smith, C. E., and Baker, E. E.: A Summary of the Present Status of Coccidioidal Infection, Weekly Bull. California Dept. Pub. Health **20**:113, 1941.

4. Emmons, C. W.: Isolation of Coccidioides from Soil and Rodents, Pub. Health Rep. **57**:109, 1942.

5. (*a*) Dickson, E. C., and Gifford, M. A.: Coccidioides Infection (Coccidioidomycosis), Arch. Int. Med. **62**:853 (Nov.) 1938. (*b*) Stiles, G. W., and Davis, C. L.: Coccidioidal Granuloma, J. A. M. A. **119**:765 (July 4) 1942. (*c*) Meleney, H. E.: Coccidioidomycosis: Public Health Implication of Tropical and Imported Diseases, Am. J. Pub. Health **34**:20, 1944. (*d*) Smith, C. E.: Coccidioidomycosis, M. Clin. North America **27**:790, 1943; Am. J. Pub. Health **30**:600, 1940.

6. Ophüls, W.: Further Observations in a Pathogenic Mould Formerly Described as a Protozoon (Coccidioides Immitis), J. Exper. Med. **6**:443, 1905.

7. (*a*) Dickson, E. C.: Coccidioides Infection, Arch. Int. Med. **59**:1029 (June) 1937. (*b*) Kessel, J. F.: Coccidioidomycosis, Am. J. Trop. Med. **21**:447, 1941. (*c*) Stiles, G. W., and Davis, C. L.: Coccidioidal Granuloma, J. A. M. A. **119**:765 (July 4) 1942. Footnote 5 *d*.

The ability to culture coccidioides from the soil and the reported accidental infection in the laboratory by inhalation of chlamydospores have directed practically all animal experimentation on infectivity by the respiratory tract toward the use of cultures containing chlamydospores.[8] That spherules when inoculated intraperitoneally, subcutaneously or intravenously do produce infection is a standard accepted fact,[9] but infection by spherules through the respiratory tract is denied. Smith and Baker [3] summarized the situation as follows:

> The spherule is not adapted to dissemination of the fungus outside of the animal body. It is pointless to isolate a patient with coccidioidal infection. This great distinction to tuberculosis cannot be overemphasized. On the other hand, spores of the mycelial form are very infective. The white mycelial thread of the test tube and presumably nature from a tiny, light spore (chlamydospore), readily wafted by the breezes.

EXPERIMENTAL PROCEDURE

This study was directed into two channels: (*a*) the determination of whether the spherule outside of the body can remain viable for a long time without the production of mycelial threads or spores and (*b*) the determination of whether sputum, pus or exudate from human sources containing spherules can produce infection in guinea pigs on instillation into the respiratory tract. Judging from the literature and from personal communication with C. E. Smith, of Stanford University, a similar study has not been reported.

Source of Spherule-Containing Material.—The spherule-containing material included (1) sputum from human sources, (2) pus from human and animal sources, (3) granulation tissue from a human source and (4) lymph nodes from a human source. The lymph nodes and granulation tissue were ground in a mortar and diluted with saline solution to make a thick emulsion possible of injection through a 19 gage needle; the sputum and pus were used without dilution.

Methods of Instillation into the Trachea of Guinea Pigs.—With the guinea pig under light ether anesthesia, a 2 cm. incision of the skin was made in the midline of the neck over the trachea. The trachea was isolated by blunt dissection and was punctured with a sharp-pointed needle (20 gage). This needle was removed, and in its place a sterile, pointless, blunt needle with smooth edges that were perpendicular to the shaft needle (19 gage, 5 cm. stem) was inserted. A syringe containing exudate was attached to the needle, and 0.15 to 0.3 cc. was instilled. The syringe was removed and replaced by a clean one. About 4 cc. of air was injected, and this was repeated three to four times to propel the exudate into the finer ramifications of the respiratory tree. The syringe was removed, and then a stylet was inserted in the needle and both removed together. The wound was flooded with 70 per cent alcohol, and the skin was approximated by a silk suture.

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8. (*a*) Ahlefeldt, F. E.: Studies in Coccidioidal Granuloma, Arch. Path. **2**:206 (Aug.) 1926. (*b*) Cronkite, A. E., and Lack, A. R.: Primary Pulmonary Coccidioidomycosis, J. Exper. Med. **72**:167, 1940. (*c*) Trager, M., and Liebow, A. A.: Intratracheal and Intraperitoneal Infection of Mouse with Coccidiodes Immitis, Yale J. Biol. & Med. **15**:41, 1943.

9. Cox, A. J., and Smith, C. E.: Arrested Pulmonary Coccidioidal Granuloma, Arch. Path. **27**:717 (April) 1939. Footnotes 6 and 8 *a*.

Animal Number	Source and Age of Material	Method of Inoculation	Coccidioidin Skin Test			D Sh oc
			Days	Dilution	Results*†	
3	Pus, 1 day (human)	Intratracheal	0	0	0	
6	Pus, 1 day (human)	Intratracheal	0	0	0	
7	Pus, 1 day (human)	Intratracheal	32	1:10	10x15 + +	
				Concentrated	30x30 ++ ++	
15	Pus, 19 days (human)	Intratracheal	0	0	0	
16	Pus, 19 days (human)	Intratracheal	13	1:10	—	
				Concentrated	8x8 Tr. Tr.	
17	Pus, 19 days (human)	Intratracheal	13	1:10	—	
				Concentrated	5x8 Tr. Tr.	
19	Pus, 19 days (human)	Intratracheal	13	1:10	5x5 Tr. Tr.	
				Concentrated	10x15 + +	
18	Pus, 19 days (human)	Intratracheal	13	Concentrated	5x5 Tr. Tr.	
			100			
			160	1:10	—	
				Concentrated	10x15 + +	
14	Pus, 6 days (animal)	Intratracheal	13	1:10	5x5 Tr. Tr.	
				Concentrated	15x20 + +	
13	Pus, 6 days (animal)	Intratracheal	13	1:10	10x10 — Tr.	
				Concentrated	15x15 + +	
1	Granulation tissue, 1 day (human)	Intratracheal	0	0	0	
2	Granulation tissue, 1 day (human)	Intratracheal	0	0	0	
8	Granulation tissue, 1 day (human)	Intratracheal	32	1:10	8x8 Tr. Tr.	
				Concentrated	20x15 + ++	
22	Granulation tissue, 110 days (human)	Intratracheal	5	1:10	—	

and Smear ultures in Guinea Pigs Subjected to Spherule-Containing Exudates

Results*†	Postmortem Examination of Animal: Gross Observations	Organ Examined	Spherules in Direct Mount in 10% NaOH †	Culture on 3% Tryptose Agar †	Histologic Observations
0	Upper lobe of right lung; middle lobes; no metastasis	Operation site	+	+	Specific granuloma with spherules
		Lung	+	+	Specific granuloma with spherules
		Lymph node	—	—	Specific granuloma with spherules
0	Apex of left lung; miliary involvement of lung, liver, kidney and spleen	Operation site	+	+	Specific granuloma with spherules
		Lung	+	+	Specific granuloma with spherules
		Lymph node	—	—	Specific granuloma with spherules
10x15 + + 50x30 ++ ++	All lobes; no metastasis	Operation site	+	+	0
		Lung	+	+	Specific granuloma
		Lymph node	—	—	Nonspecific reaction
0	Apexes of upper lobes and lower lobe of left lung; no metastasis	Operation site	—	—	—
		Lung	0	0	Specific granuloma
		Lymph node	—	+	Nonspecific reaction
— 8x8 Tr. Tr.	All lobes; no metastasis	Operation site	+	+	0
		Lung	+	+	Specific granuloma
		Lymph node	+	+	Nonspecific reaction
— 5x8 Tr. Tr.	All lobes; no metastasis	Operation site	—	0	—
		Lung	+	+	Specific granuloma
		Lymph node	0	0	0
5x5 Tr. Tr. 10x15 + +	All lobes; no metastasis	Operation site	0	0	—
		Lung	+	+	Specific granuloma
		Lymph node	0	+	Nonspecific reaction
5x5 Tr. Tr. — 10x15 + +	All lobes; no metastasis	Operation site	—	—	—
		Lung	0	0	Specific granuloma
		Lymph node	0	0	Nonspecific reaction
5x5 Tr. Tr. 15x20 + +	Both lobes of left lung; no metastasis	Operation site	—	—	—
		Lung	+	+	Specific granuloma
		Lymph node	—	—	Nonspecific reaction
10x10 — Tr. 15x15 + +	Apexes of upper lobes; no metastasis	Operation site	+	—	0
		Lung	+	+	Specific granuloma
		Lymph node	—	—	Nonspecific reaction
0	Two lobes (subapical) no metastasis	Operation site	+	+	Specific granuloma
		Lung	+	0	Specific granuloma with spherules
		Lymph node	—	0	Nonspecific reaction
0	Three lobes; both apexes; lesion in spleen	Operation site	+	—	Specific granuloma
		Lung	0	+	Specific granuloma
		Lymph node	0	+	0
8x8 Tr. Tr. 20x15 + ++	Middle lobe of right lung; no metastasis	Operation site	+	+	Specific granuloma with spherules
		Lung	0	0	Nonspecific reaction
		Lymph node	+	0	Nonspecific reaction
—	Single nodule; no metastasis	Operation site	—	—	—
		Lung	+	0	Specific granuloma
		Lymph node	—	—	Nonspecific reaction

Animal Number	Source and Age of Material	Method of Inoculation	Coccidioidin Skin Test			Du... Size... cent...
			Days	Dilution	Results*†	
21	Granulation tissue, 110 days (human)	Intratracheal	5 13 19	1:10 1:10 1:10	— — —	2... (d...
20	Granulation tissue, 110 days (human)	Intratracheal	25 39 70 	1:10 1:10 Concentrated	— 8x8 + + 10x15 + +	2... (k... Four
24	Sputum, 3 days (human)	Intratracheal	21	Concentrated	—	2... (k... Two mi...
25	Sputum, 3 days (human)	Intratracheal	21	Concentrated	—	2... (k... Two
26	Sputum, 3 days (human)	Intratracheal	21	Concentrated	—	2... (k... One u...
27	Sputum, 3 days (human)	Intratracheal	21	Concentrated	—	2... (k... Two
28	Sputum, 3 days (human)	Intratracheal	21	Concentrated	—	2... (k... Two
29	Sputum, 3 days (human)	Intratracheal	21	Concentrated	—	3... (d... All lo...
4	Lymph node, 1 day (human)	Intratracheal	0	0	0	1... (d... Two l... to s...
5	Lymph node, 1 day (human)	Intratracheal	0	0	0	1... (d... Two l... to s...
9	Lymph node, 1 day (human)	Intratracheal	0	0	0	3... (k... Three ... meta...
23	Lymph node, 110 days (human)	Intratracheal	13 40	1:10 1:10	— 8x10 + +	7... (k... No les...
10	Pus, 1 day (human)	Intraperitoneal	0	0	0	1... (d... Miliary ... heart
11	Granulation tissue, 1 day (human)	Intraperitoneal	0	0	0	2... (d... Miliary ... testi...
12	Lymph node, 1 day (human)	Intraperitoneal	32 180	1:10 Concentrated Concentrated	8x8 Tr. Tr. 18x20 ++ ++ 20x30 ++ ++	1... (k... Subple...

* Numbers signify millimeters, and Tr. means trace to 4 plus; top reading indicates redness and bottom reading, indura...
† + indicates a positive reaction; — a negative reaction, and 0, not done.

...tures in Guinea Pigs Subjected to Spherule-Containing Exudates—Continued

	Postmortem Examination of Animal			
Gross Observations	Organ Examined	Spherules in Direct Mount in 10% NaOH †	Culture on 3% Tryptose Agar †	Histologic Observations
0	Operation site	0	0	0
	Lung	—	+	0
	Lymph node	—	—	0
Four lobes; no metastasis	Operation site	—	0	—
	Lung	0	+	Specific granuloma
	Lymph node	0	0	Nonspecific reaction
Two lobes of left lung (upper and middle); no metastasis	Operation site	—	+	0
	Lung	—	—	Pneumonia; no spherules
	Lymph node	+	+	Nonspecific reaction
Two upper lobes; no metastasis	Operation site	—	—	0
	Lung	—	+	Interstitial pneumonia; no spherules
	Lymph node	+?	—	Nonspecific reaction
One upper lobe; no metastasis	Operation site	0	0	No lesion
	Lung	—	—	Interstitial pneumonia; no spherules
	Lymph node	—	—	Nonspecific reaction
Two upper lobes; no metastasis	Operation site	0	0	0
	Lung	—	+	Interstitial pneumonia; no spherules
	Lymph node	+	0	Nonspecific reaction
Two upper lobes; no metastasis	Operation site	0	0	0
	Lung	—	—	Interstitial pneumonia; no spherules
	Lymph node	—	—	Nonspecific reaction
All lobes	Operation site	—	+	0
	Lung	—	—	Granuloma; no spherules
	Lymph node	—	+	Nonspecific reaction
Two lobes of left lung; metastasis to spleen; no spherules	Operation site	+	+	Specific granuloma
	Lung	+	+	Specific granuloma
	Lymph node	+	+	Specific granuloma
Two lobes of left lung; metastasis to spleen; no spherules	Operation site	+	+	Specific granuloma
	Lung	+	+	Specific granuloma
	Lymph node	+	+	Specific granuloma
Three lobes of right lung; no metastasis	Operation site	+	+	Specific granuloma
	Lung	+	+	Specific granuloma
	Lymph node	—	—	Nonspecific reaction
No lesions; no metastasis	Operation site	0	0	No lesion
	Lung	0	0	No lesion
	Lymph node	0	0	No lesion
Miliary to lung, liver, spleen and heart	Peritoneum	+	+	0
	Mesenteric	+	+	Specific granuloma
	Lymph node			
Miliary to lung, liver, spleen and testicle	Peritoneum	+	+	0
	Testicle	+	+	Specific granuloma
	Meninges	0	—	0
Subpleural nodule; no metastasis	Lung	0	0	Specific granuloma; no spherules
	Lymph node	0	0	Nonspecific reaction

Twenty-six guinea pigs were used for intratracheal instillation and 3 for intraperitoneal inoculation. The skin of the animals was tested with a 1:10 dilution of coccidioidin (0.1 cc.) at the onset of the experiment, and it was retested at varying intervals during the experiment with 1:10 and concentrated dilutions. The animals were killed at intervals of eight to one hundred and sixty-five days (7 animals died fourteen to sixty-five days after the onset of the experiment). At autopsy, emulsions of material from the lungs, regional lymph nodes and site of injection were digested in 10 per cent sodium hydroxide and examined microscopically; cultures were made of material from the lungs, regional lymph nodes and site of injection on 3 per cent tryptose agar plates. Sections were taken of the lungs, draining lymph nodes, liver, spleen, kidneys, site of operation and cervical lymph nodes and stained with hematoxylin and eosin.

Method of Aging Spherule-Containing Exudates.—All materials were placed in test tubes and kept refrigerated at 12 C. There was frequent exposure to light, as the refrigerators were opened at numerous times during the day. At varying intervals up to one hundred and ten days direct mounts in 10 per cent sodium hydroxide, culture on 3 per cent tryptose agar plates and instillations into guinea pigs were done. Into 9 animals were instilled one day old, into 5 nineteen day old and into 4 one hundred and ten day old pus, granulation tissue and lymph node emulsions from a human source. Two animals received one day old pus from an infected guinea pig. Into 6 animals were instilled one day old sputum, and 3 animals received intraperitoneal injections of two day old pus from a human source.

In other experiments now in progress,[10] spherule-containing sputum is being exposed out-of-doors in the sun and in the shade, with and without soil.

RESULTS

A. *Lesions Produced After Intratracheal Instillations of Spherule-Containing Exudate.*—The table summarizes the results in the 26 animals; the lesions produced in the lungs varied from well defined but irregular nodules 2 to 3 mm. in diameter to involvement of a portion or of an entire lobe (fig. 4). On section these areas were grayish white, with well defined borders and granular surfaces. Occasionally there was a small yellow fleck resembling pus in the center of some of these nodules. One or two lobes were usually involved, but in some instances all lobes were included. In practically every instance the upper lobes contained lesions. Less frequently the lower lobes were involved. The regional lymph nodes in the hilus and paratracheal regions were uniformly enlarged up to 1 to 3 cm. in diameter. On section the lymph nodes were uniformly gray to pinkish gray, with grayer zones in the cortices. The spleen was usually enlarged. Gross lesions were not seen in the liver, spleen or kidneys. In the first group of animals, before the technic was perfected, localized abscesses or zones of induration were found in the neck at the site of operation. With improvement of technic, no local lesions were noted.

10. Rosenthal, S. R., and Elmore, F. H.: Fate of Spherules in Nature, to be published.

Microscopic Examination: Lung: The lesions were those of bronchopneumonia and interstitial pneumonia (fig. 5). The exudate in the alveoli varied from fibrin and pus cells to sheets of swollen epithelioid cells. Spherules in every stage of development were noted in the exudate. In the 6 animals into which sputum was instilled, only ghosts of spherules were noted. The interstitial reaction consisted mainly of swollen histiocytes, fibrin and spherules. When the spherule's external membrane was interrupted, pus cells appeared. Giant cells were common and usually were of the foreign body type. These cells frequently contained one or more spherules or spores and seemed to be the centers for epithelioid cell granulomas. Rarely, small abscesses were noted, in which degenerated pus cells occupied the center.

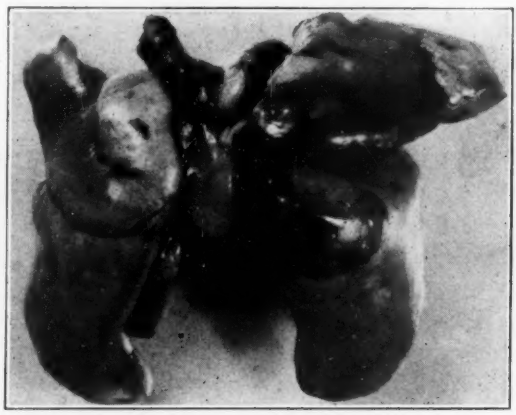

Fig. 4.—Pneumonic lesion of portions of upper and lower lobes of the right lung following intratracheal instillation of spherule-containing exudate in the guinea pig. Note enlarged hilar lymph nodes.

Hilus and Paratracheal Lymph Nodes: The most common finding was wide marginal sinuses filled with swollen histiocytes, pus cells and round cells. The follicles were prominent and had large germinal centers Occasionally granulomas composed of epithelioid cells with central necrosis or pus cells were noted in the marginal sinuses, extending into the cortex and medulla. Only rarely were spherules seen in these granulomas. At times a spherule could be found, with capsule intact, contained within a swollen giant cell or epithelial cell, without any other reaction. In less than one third of the cases spherules were noted in the nodes, although the pulmonary involvement was constant and usually extensive.

Spleen: Discrete nodules of central necrosis or pus cells surrounded by epithelial cells were occasionally noted; spherules were rare. With improvement of technic, in animals in which no lesions were noted at the site of operation the spleen remained free of involvement.

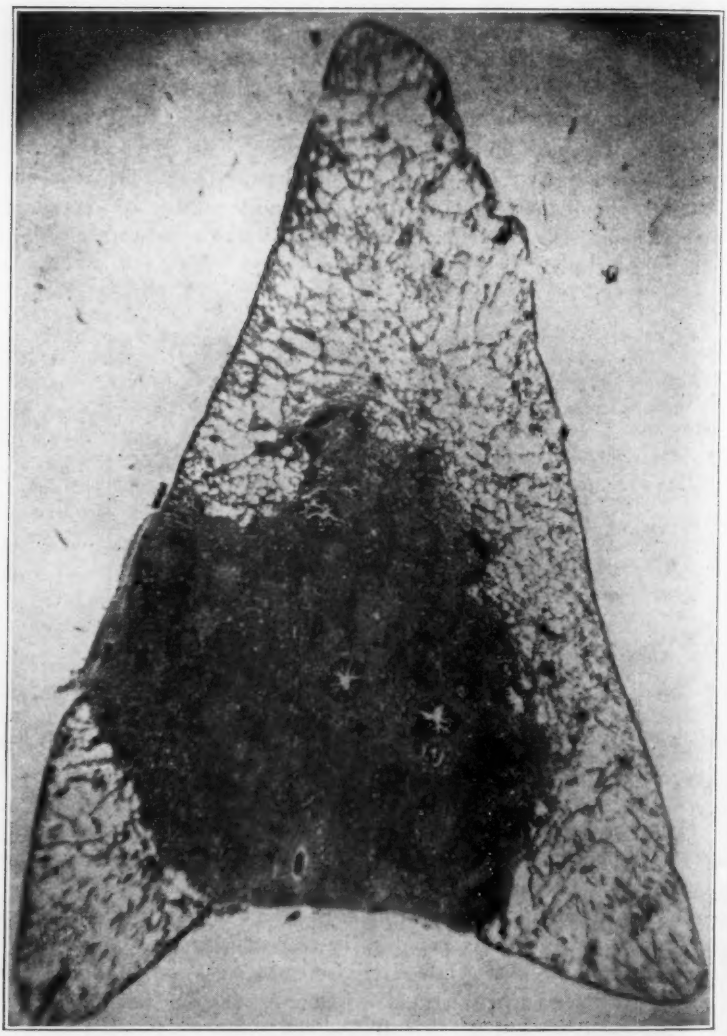

Fig. 5.—Microscopic section of entire lobe of guinea pig, showing primary focal pneumonia following intratracheal instillation of spherule-containing exudate. × 14.

Liver and Kidneys: Specific granulomas were found in only 1 case. They resembled specifically granulomas of the spleen. The animal involved had a local cervical lesion with many spherules.

B. *Results in Animals Inoculated Intraperitoneally.*—In contrast to those inoculated intratracheally, of the 3 animals given intraperitoneal injections the 2 killed at eighteen and twenty days presented extensive miliary involvement of the liver, spleen, kidneys, lungs and myocardium. Spherules were found in large numbers in all organs. The pulmonary lesions were pinpoint to pinhead in size and discrete. Histologically, they were perivascular, well defined granulomas with epithelioid cells, giant cells and occasional pus cells. The bronchi were free. One animal, killed after one hundred and eighty-four days, presented a single small subpleural nodule, which on microscopic examination resembled a specific granuloma without spherules. The other organs were free from involvement.

C. *Results of Aging Spherule-Containing Exudates.*—Direct mounts in 10 per cent sodium hydroxide and cultures on tryptose agar of the spherule-containing exudates kept in the cold at varying intervals from one to one hundred and ten days revealed spherules at all times. No hyphae or chlamydospores were noted at any time. The spherules appeared plasmolyzed or distorted; yet cultures yielded few colonies after a long period of incubation.

In the sputum exposed out-of-doors, both spherules and typical hyphae producing chlamydospores were observed in a fair percentage of the 60 specimens examined. The completed data are as yet not available.

In the group of 17 animals in which one to nineteen day old material was used direct examination of the emulsion of the material from the lungs of 13 yielded spherules in all. Of the 16 pulmonary cultures, 11 were positive. The draining lymph nodes on direct examination yielded spherules in 4 of 13 animals; 6 cultures were positive. Because of a misunderstanding, in the 6 animals into which sputum was instilled examinations were not made until three days after autopsy. In 4 of the 6 animals, nevertheless, culture of material from the lungs or lymph nodes gave positive results. Of the 4 animals inoculated with one hundred and ten day old material, typical granulomas resulted in 2. Cultures of material from the lungs of these 2 animals yielded spherules. Cultures of material from the animals killed at one hundred and sixty-five days (intratracheal group) and one hundred and eighty-five days (intraperitoneal group) were sterile.

COMMENT

The results indicate that spherule-containing pus, sputum, granulation tissue and lymph node emulsions of material from human sources when instilled into the trachea of animals produce localized and diffuse

lesions of the lungs, with the corresponding lymph node component. Involvement in animals resembles closely that in human beings in that it is localized in the lungs, especially the upper lobes, has a corresponding involvement of the lymph nodes and is rarely generalized. Passage from animal to animal by the intratracheal route was also accomplished. Spherule-containing exudates under certain conditions will retain viable spherules without producing hyphae and chlamydospores.

It cannot be denied that infectivity of coccidioidomycosis is brought about in a large measure from other than human contact. The fact that 10 per cent of the entire Western Flying Command established in remote centers of the Southwest gave positive reactions to skin tests with coccidioidin and that in some stations 80 per cent of the population reacted positively (when in residence longer than six months[11]) is indeed convincing evidence. The rodent reservoir suggested by Emmons[4] warrants serious consideration. However, these findings do not exclude the possibility of contagiousness. In the past, writers failed to observe person to person contagion because only the generalized form of coccidioidomycosis was recognized. Coccidioidomycosis granuloma is a rare disease, as only 450 cases were reported in California up to July 1936. When Dickson[7a] in 1937 pointed out that a number of respiratory diseases, diagnosed as "valley fever" or "desert rheumatism" or under other names were also caused by C. immitis, the widespread and endemic nature of the disease was first realized. The noncontagious view is still accepted, albeit the evidence presented in the literature is meager.[12]

Preliminary studies indicate that hyphae and chlamydospores may form in outdoor exposure of sputums, with or without soil. Thus both types of spores may be implicated as sources of infection. The respiratory tree is susceptible to the spherule as well as to the chlamydospore. The foregoing facts point to the contagiousness as well as to the infectivity of coccidioidomycosis. Although more positive evidence of transmission from patient to patient and animal to animal is necessary, until proved otherwise the disease should be considered contagious.

SUMMARY

1. The spherules of C. immitis remain viable under certain conditions and do not produce hyphae and chlamydospores in exudates from human sources for at least one hundred and ten days (experiments still in progress).

11. Lee, R. V.: Coccidioidomycosis in the Western Flying Command, California & West. Med. **61**:133, 1944.

12. Jacobson, H. D.: Coccidioidal Granuloma, California & West. Med. **29**:392, 1928. Smith, C. E.: Personal communication to the author; footnote 5 *d*.

2. By instilling spherule-containing sputum or exudates from human or animal sources into the bronchi of guinea pigs and propelling them by air pressure into the finer ramifications of the bronchioles and alveoli, it is possible to produce coccidioidomycosis in 100 per cent of the animals.

3. The lesions are localized for the most part in the upper portions of the lungs, are single or multiple, have a lymph node component and are not generalized, thus simulating the human infection.

4. These experiments show that spherules (or sporangia) can be infective through the respiratory route from man to animal and from animal to animal.

5. It is concluded that active primary or progressive coccidioidomycosis in human beings should be considered contagious until proved otherwise.

OSTEOGENESIS IMPERFECTA

A Study of Five Generations

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THE PURPOSE of this paper is to report a family in which five generations have been affected with osteogenesis imperfecta. Riesenman and Yater,[1] after a study of seven families, concluded that osteogenesis imperfecta (fragilitas osseum, Lobstein's disease or Vrolik's disease) is "a hereditary and familial disease and is transmitted as a dominant mendelian factor. It is a hereditary mesenchymal hypoplasia due to a disturbance of the gene or genes that determine normal mesenchymal development."

Lobstein is generally given credit for first describing this disease, but Riesenman and Yater [1] ascribed the first description to Elman in 1788. Lobstein's syndrome today is called osteogenesis imperfecta tarda in contradistinction to the syndrome described by Vrolik in 1849. The latter, at present, is referred to as the early or congenital form. Spurway [2] in 1896 called attention to the fact that certain patients with fragile bones also had blue scleras. Bronson [3] in 1917 noted familial deafness in persons with brittle bones and blue scleras. In 1926 Key [4] added hypertonicity of the ligaments and hypermotility of the joints to complete the clinical picture of osteogenesis imperfecta. The family studies under consideration show a high incidence of exophthalmos. The decision as to whether this feature is also part of the syndrome or whether the trait is peculiar to the family studies must await further reports.

REPORT OF CASES

The family was of French ancestry and was composed of frail, small-statured persons. The largest was 5 feet 7 inches (170 cm.) tall. All the patients represented in cases 2 to 9 and 13 to 15 inclusive were examined by me, and information on other members of the family was furnished by patients seen personally. Some

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From the Department of Medicine, Toledo Hospital.

1. Riesenman, F. R., and Yater, W. M.: Osteogenesis Imperfecta, Arch. Int. Med. **67**:950 (May) 1941.

2. Spurway, J.: Hereditary Tendency to Fractures, Brit. M. J. **2**:844, 1896.

3. Bronson, E.: On Fragilitas Osseum and Its Association with Blue Sclerotics and Otosclerosis, Edinburgh M. J. **18**:240, 1917.

4. Key, J. A.: Brittle Bones and Blue Sclerae, Arch. Surg. **13**:523 (Oct.) 1926.

members of the family were inaccessible for roentgen examination. The persons represented in cases 19, 20, 21, 22 and 23 cannot be considered in this study since no information could be secured.

Roentgenographic studies were conducted by Dr. Murray C. Goodrich, of the x-ray department of the Toledo Hospital. For each of the adults studies were made of the pelvis, the lower extremities, one pectoral girdle and one humerus. For the children studies were made of the entire body.

CASE 1.—The patient, a man, died when 53 years of age, after having twenty-seven fractures. Most of the fractures were incurred in childhood. He had severe kyphoscoliosis and lateral bowing of the femurs.

CASE 2.—A 73 year old woman had had four fractures of the left femur during her childhood. She was deaf and had been so for many years. Her scleras were

Age and Sex Distribution of the Various Manifestations of Osteogenesis Imperfecta

Case	Age	No. of Fractures		Blue Scleras		Deafness		Exophthalmos		Height	Weight, Lb.
		M.*	F.*	M.	F.	M.	F.	M.	F.		
1	53 yr.	27	..	..	..	..	..	..	..	4′ 8″	
2	73 yr.	..	4	..	1	..	1	..	..	5′	124
3	51 yr.	..	..	..	1	..	..	..	1	5′ 2″	130
4	54 yr.	4	..	1	..	..	..	..	..	5′ 3″	150
5	3 days	2	..	..	..	..	..	..	..	.....	...
6	29 yr.	..	..	..	1	..	..	..	1	4′ 11″	97
7	26 yr.	..	7	..	1	..	1	..	1	4′ 3″	90
8	27 yr.	..	..	..	1	..	..	..	1	5′ 7″	130
9	25 yr.	..	2	..	1	..	1	..	1	5′ 2″	109
10	19 yr.	..	4	..	1	..	..	..	..	5′ 4″	117
11	21 yr.	..	..	..	..	..	..	..	..	5′ 6″	122
12	23 yr.	..	..	..	..	..	..	..	..	5′ 2″	108
13	6 yr.	10	..	1	..	..	..	1	..		
14	3 yr.	..	3	..	1	..	..	..	1		
15	3 mo.	..	..	1	..	..	..	1	..		
16	5 yr.	..	..	..	..	..	..	..	..		
17	3 yr.	..	..	..	..	..	..	..	..		
Totals.....		43	20	3	8	..	3	2	6		

* M. indicates males and F. females.

blue, as were her tympanic membranes. Roentgenograms of the pelvis and long bones revealed a large amount of callus in the upper third of the left femur. There was no lateral bowing. Many cystic areas gave it a honeycombed appearance. The femoral epiphysis was wide and also had a honeycombed appearance.

CASE 3.—With the exception of blue scleras and exophthalmos, the 51 year old woman in this case had none of the characteristic findings of osteogenesis imperfecta.

CASE 4.—The patient, a 54 year old man, had blue scleras. When he was a child he fractured his left femur three times and his right humerus once.

CASE 5.—The patient in this case was a boy born with severe kyphoscoliosis and bilateral clavicular fractures; he lived only three days.

CASE 6.—A 29 year old woman had blue scleras and pronounced exophthalmos but had had no fractures.

CASE 7.—A 26 year old woman had had seven fractures, two of the left femur and five of the right femur. All of these fractures followed slight trauma. When the patient was 11 years old she had a parathyroidectomy as well as a partial thyroidectomy, and since that time she had had only one fracture. Whether the

operation or puberty arrested the tendency to fracture cannot be determined. She had definite exophthalmos, china blue scleras and blue tympanic membranes, and she was deaf. There was a 5 inch (12.5 cm.) shortening of the left leg and considerable lateral bowing of both femurs. Roentgenograms of these bones revealed deformity, with lateral bowing, diminished density of the bone, thin cortices, large deposits of callus and a honeycombed appearance. The changes were present also in the tibia, the fibula, the lower end of the humerus, the upper ends of the radius and ulna and all the tarsals and metatarsals.

Case 8.—The patient, a 27 year old woman, had had no fractures. She had blue scleras, blue tympanic membranes and exophthalmos.

Case 9.—A 25 year old woman had had two traumatic fractures. She was becoming progressively deaf, but did not use a hearing aid. She had blue scleras and blue tympanic membranes as well as exophthalmos.

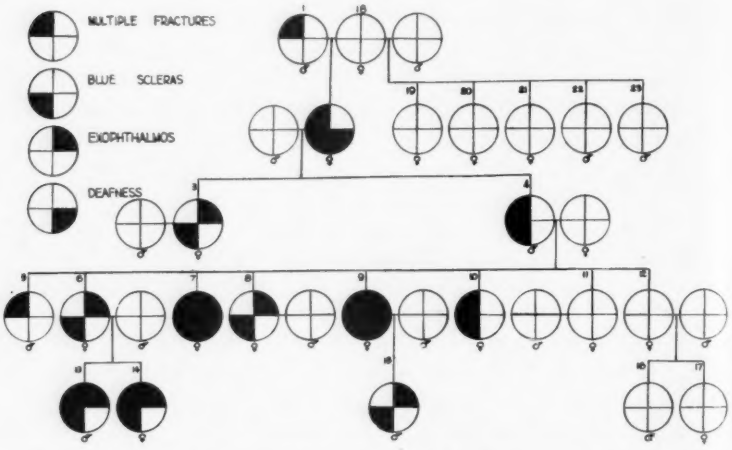

Fig. 1.—Genealogic table showing graphically the changes seen in osteogenesis imperfecta.

Case 10.—A 19 year old woman had had four fractures, three of the right femur and one of the right arm. These fractures all occurred in childhood. She had blue scleras.

Case 13.—The patient was a 6 year old boy who was admitted to the Toledo Hospital on May 3, 1946, with his tenth fracture. He had then had six fractures of the left femur and four fractures of the right femur. He had bilateral femoral fractures at the age of 2, when he kicked his cradle. Other fractures had occurred at various intervals through the same fracture sites and were brought about by slight trauma. He was a fairly well developed and well nourished white boy. His head had prominent parietal bosses. The scleras were blue, and there was prominent exophthalmos; the tympanic membranes were blue. The thorax was increased in anteroposterior diameter, and there was a fairly prominent Harrison groove. The extremities showed marked lateral bowing of the right femur and slight lateral bowing of the left femur.

Laboratory Data.—The red blood cell count was 4,480,000, with a hemoglobin content of 13.2 Gm. per hundred cubic centimeters, and the white blood cell count was 9,400, with a normal differential count. The daily specimens of urine gave a 3 to 4 plus Sulkowitch reaction for calcium. The serum calcium was 10.2 mg. per hundred cubic centimeters on one occasion and 9.7 mg. on another. The serum phosphorus was 5.6 mg. per hundred cubic centimeters on one occasion and 6.0 mg. on another. The alkaline phosphatase was 7.3 and 9.8 Bodansky units on two occasions.

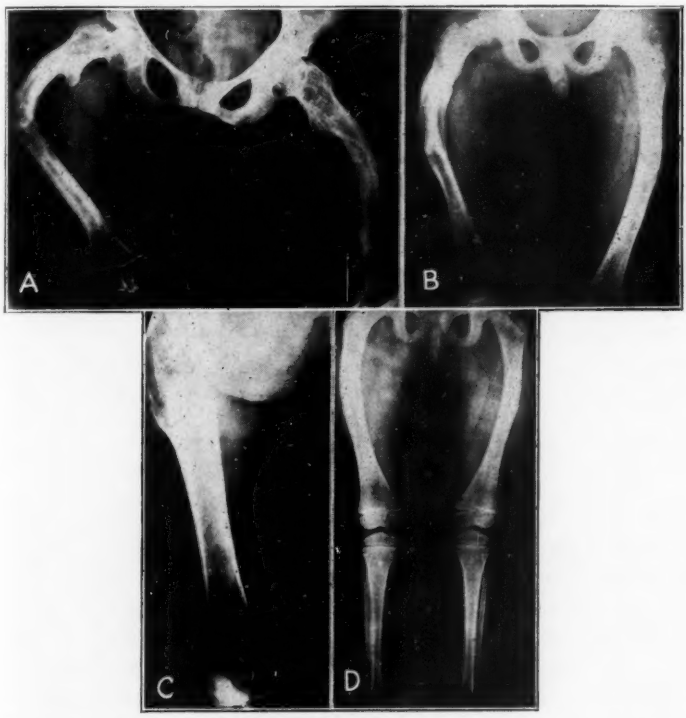

Fig. 2.—Representative roentgenograms in cases 2, 7, 13 and 14. *A* (case 7) shows pronounced changes, with lateral bowing, honeycombed areas of Fairbanks, thin cortices, generalized decalcification of the bones and lateral displacement of the medullary cavities. *B* (case 13) shows lateral bowing of both femurs following multiple fractures as well as the changes seen in case 7. *C* (case 2) shows generalized decalcification of the long bones, with a large amount of callus in the upper third of the left femur. *D* (case 14) is a roentgenogram of the lower extremities taken before the fracture, showing decreased density of bones and slight lateral bowing of the femurs.

Course in the Hospital.—The left femur was put up in a modification of Buck's extension with overhead traction, and within a few days the patient was able to assume a sitting position. A roentgenogram showed the typical changes of lateral bowing, excessive callus formation, honeycombed bone, thin cortices of the affected bones and a lateral displacement of the medullary cavity of the affected bones in

the fractured areas. After six weeks in this traction the patient was put in a spica cast and sent home.

He has since sustained a fracture of the left femur on Feb. 3, 1947, and one of the right femur on May 12. These were fractures number 11 and 12 respectively. Both followed minor trauma, and both occurred through the old fracture sites. They were treated, as before, with Buck's extension and overhead traction.

CASE 14.—A 3 year old girl entered the Toledo Hospital three days after her brother (the patient in case 13) had left, with her third fractured femur. When this child was 2 months old she also suffered a bilateral femoral fracture when she kicked the cradle. Since that time she had been active but had had no fractures. On the day of her admission to the hospital she slipped on a rug and fractured her left femur. Physical examination revealed no abnormalities except for blue scleras, blue tympanic membranes and decided exophthalmos. The findings in laboratory studies were normal. Roentgenograms made before the fracture revealed a definite tendency to fragile bones, but there was only slight bowing of the femurs and thinning of the cortices. A roentgenogram taken on admission showed a fracture of the midshaft of the left femur, with no displacement but with slight lateral bowing. The cortex in the region of the fracture was not unusually thin. The patient was given the same treatment as her brother, and at the time of the writing of this paper she was progressing well.

CASE 15.—The patient, a 3 month old boy, had had no fractures. He had blue scleras. Roentgenologic studies of the bones revealed none of the characteristic findings of osteogenesis imperfecta.

OTHER CASES.—The patients in cases 19, 20, 21 and 22 were children of the patient in case 18 by a second marriage. The patient in case 2 did not live with these children but was adopted by another family and thus lost track of her half brothers; she could remember no abnormalities in these people.

COMMENT

The cause of osteogenesis imperfecta is unknown, but it is assumed that there is some hereditary inferiority of the mesenchyme. Hill and McLanahan noted [5] that many other tissues of mesenchymal origin are not affected and that abnormalities have also been observed in tissues of endodermal and ectodermal origin. Farber and Margulis [6] expressed the opinion that the condition may be due either to some development defect or to a metabolic dysfunction or to both. They also stated that the poor mineralization of the bones may be due to an excessive excretion of calcium, a deficient absorption of calcium or an idiosyncrasy of alimentation. Other authors have suggested that there is a faulty metabolism which results from various endocrine upsets. Rosenbaum [7] stated that, while none of the endocrine organs can be incriminated per se, he has had some success in the treatment of patients with osteogenesis imperfecta

5. Hill, R. G., and McLanahan, S.: Brittle Bones and Blue Sclerae in Five Generations, Arch. Int. Med. **59**:41 (Jan.) 1937.

6. Farber, J. E., and Margulis, A. E.: Blue Sclerae, Brittle Bones and Deafness, Arch. Int. Med. **71**:658 (May) 1943.

7. Rosenbaum, S.: Osteogenesis Imperfecta and Osteopsathyrosis, J. Pediat. **25**:167, 1944.

by administration of anterior pituitary extracts. Hennessy [8] has found the endocrine organs to be normal at necropsy.

Some of the writers divide this disease into two or three types—congenital, late and idiopathic. There is a difference of opinion as to whether the conditions described under the terms of osteogenesis imperfecta congenita and osteogenesis imperfecta tarda, hereditary and nonhereditary osteopsathyrosis, fragilitas osseum, brittle bones and blue scleras represent the same disease and as to the propriety of labeling them simply as osteogenesis imperfecta. Rosenbaum [7] quoted Glanzmann and Funk, who both stated that the two forms of this disease are separate entities and never occur in the same family. Rosenbaum then cited 5 cases which prove that the early and late types are both manifestations of the same disease. In the present study there was 1 patient (case 5) in whom the disease was of the so-called congenital type. This child was born with a kyphoscoliosis and fractures of both clavicles and lived only three days. In the other children the manifestations of the disease did not develop until later in life. Chont [9] also reported a similar situation in the families he studied. According to Glanzmann and Funk, the congenital form is not hereditary, while the Lobstein type is hereditary. The congenital type is considered to be a recessive trait, and thus it is possible for either form of the disease to be manifested in any one family. Even when the trait is dominant, its manifestations may vary from generation to generation. This problem is still a moot one.

Bell pointed out that females are especially susceptible to the condition and constitute 55 per cent of all patients.[10] The female is assumed to transmit the disease. The present study appears to confirm this observation. If all the manifestations are considered, 8 of the 11 females (73 per cent) were affected. Of the 8 females, all (100 per cent) had blue scleras, 5 (62 per cent) had multiple fractures, 3 (37 per cent) were deaf and 6 (72 per cent) had definite exophthalmos. Every child and grandchild of the patient in case 3 has a stigma of the disease. Only 1 child of the patient in case 4 has any of the stigmas.

It would be expected that 50 per cent of the offspring of a heterozygotic person with this condition mated with a normal person would have blue scleras and brittle bones. This was demonstrated to be true in many series of cases [10] and is borne out in the present study. Hill and McLanahan [10] concluded that each affected person has an affected parent and that the affected person, in turn, will have an equal number of affected and unaffected children. The unaffected children will not have affected descendants. A generation is never skipped.

8. Hennessy, J. P.: Osteogenesis Imperfecta, Am. J. Obst. & Gynec. **25**:590, 1933.

9. Chont, L. K.: Osteogenesis Imperfecta, Am. J. Roentgenol. **45**:850, 1941.

10. Hill and McLanahan,[5] p. 44.

The pathology of this disease has been adequately discussed elsewhere.[11] There is an apparent decrease in the number and efficiency of osteoblasts.

There are no typical laboratory findings in this condition. Puppel and others [12] report an increase in the blood iodine and also an increase in the urinary excretion of iodine. The calcium and phosphorus levels of the blood are variable. The level of serum phosphatase is slightly elevated, and there is usually a strongly positive Sulkowitch reaction.

The appearance of the bones in roentgenograms in osteogenesis imperfecta varies according to the number of fractures the patient has sustained. Chont [9] discussed adequately the roentgenographic changes. The changes consist of generalized decalcification of the long bones, and deformation of the skulls of infants and adolescents, with an increase in the size of the cranial vault, prominent frontal and occipital bones and an increase in the number of wormian bones in some children. Early in the course of the disease there is a thinning of the cortex of the long bones. By the time the patient reaches the age of 5 or 6, the shafts have become thinner, but the width of the epiphysis remains normal, giving the bone a peculiar elongated appearance.

Following fractures, many of the bones are bent and there may be displaced fragments. The fractures are usually subperiosteal, with angulation of the fragments. With repeated fractures, there is a lateral displacement of the medullary canal at the site of the deformity. There are also narrow, transverse, triangular, decalcified, structureless areas extending a variable distance into the shaft from the convex side of the bent bone.

The bone trabeculation is scanty. Later in the course of the disease the cortex becomes thicker, with narrowing of the medullary canal and a "brittle" appearance of the affected bone.

In older children there may be the "honeycombed" bone type of Fairbanks. These bones are characterized by their extreme fragility and by the presence of cystic unossified areas. The honeycombed parts occur only after repeated fractures at the same site, and the areas of degeneration evidently follow bleeding into the bony structures.

Fractures occur in the proximity of the epiphysial-metaphysial junction. The metaphysis becomes thinner just before it reaches the epiphysial line and may account for fractures at this site.

After puberty, fractures occur less frequently. Comminuted and compound fractures are seldom observed, and nonunion is rare. Subperiosteal fractures with rotation of the fragments are common.

11. Key.[4] Chont.[9]

12. Puppel, I. D.; Barron, L. E., and Curtis, G. M.: The Nature of Osteogenesis Imperfecta, Am. J. M. Sc. **190**:756, 1935.

Deformities are due to malunion rather than to softening of the bone, and hence reduction and care of the patient are important. Buck's extension with overhead traction seems to be more desirable than immobilization of the fractured extremity in a cast.

The deafness which is associated with this disease is caused by involvement of the otic capsule, which heals with sclerosis and produces a bony ankylosis of the stapediovestibular joint impairing the transmitting system of sound waves to the internal ear.[9] It usually appears after the age of 20 and is progressive. No method of treatment has been successful.

The prognosis depends on several factors. If the patient can live a sheltered life, a minimum of fractures occur. If fractures do occur, proper care in reduction and immobilization may obviate deformities.

Persons who marry into families with osteogenesis imperfecta or persons who marry out of such families should be fully aware of the dangers to prospective children.

The treatment is largely empiric. Every form of medication has been tried, without outstanding results. Some authors report good results with the use of anterior pituitary extracts. Attempts to incriminate and remove various glands of internal secretion, such as the parathyroids and the thymus, have not been successful. Prophylaxis against injury and adequate reduction of the fragments when fractures occur represent the best form of treatment.

SUMMARY

Osteogenesis imperfecta occurring in a family of 17, representing five generations, has been studied. Roentgenographic studies were made on 9 of the 17, representing four generations. Of the 9 studied, 5 had evidences of recent or old fractures, and their bones showed typical changes of osteogenesis imperfecta. The remaining 4 revealed some of the other stigmas of the disease, but the bones were normal in appearance.

The members of this family showed the usual stigmas of osteogenesis imperfecta—blue scleras, brittle bones, deafness and hypertonicity of the ligaments. There was also a high incidence of exophthalmos.

NEUROLOGIC MANIFESTATIONS OF INFECTIOUS MONONUCLEOSIS

With Special Reference to the Guillain-Barré Syndrome

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INFECTIOUS mononucleosis has become a well known entity. The literature contains several articles describing in detail the classic clinical pictures. However, in cases which do not conform to the usual description the diagnosis is often confused or missed. In particular, this may be true when the symptoms are predominantly neurologic.

The involvement of the central nervous system may manifest itself by severe headaches, cranial nerve palsies, cerebellar signs and peripheral neuropathies. Thus there arises confusion with other diseases wherein neurologic symptoms are found. Infectious mononucleosis must be considered in the differential diagnosis of various types of lymphocytic meningitis, encephalitis, poliomyelitis, polyneuritis and the Guillain-Barré syndrome.

The Guillain-Barré syndrome was originally described as a peripheral radiculoneuritis, with findings of an increased protein level in the spinal fluid, associated with a normal or only slightly elevated white blood cell count. Symptoms of meningitis or meningoencephalitis with involvement of the cranial nerves are often present. There is considerable evidence at present that several agents or diseases can be responsible for the production of the symptom complex of infectious neuronitis. For a more detailed discussion of the etiology of the Guillain-Barré syndrome and symptoms used in connection with it, the reader is referred to the review by Pullen and Sodeman.[1]

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1. Pullen, R. L., and Sodeman, W. A.: Infectious Polyneuritis (Guillain-Barré Syndrome), Am. J. M. Sc. **211**:110 (Jan.) 1946.

The following presentation of cases is of interest in that the Guillain-Barré symptom complex developed in patients suffering from infectious mononucleosis. Neurologic complications led to death in both instances. An opportunity was presented to study the morbid anatomy encountered in infectious mononucleosis, a disease usually considered to be benign. The diagnosis was made on the basis of the postmortem findings and was substantiated in the first patient by a strongly positive reaction to the heterophile antibody test.

REPORT OF CASES

CASE 1.—A 22 year old white man was admitted to the Army Air Forces Station Hospital, Seymour Johnson Field, on Sept. 19, 1945, with the chief complaints of headache and fever. Eleven days prior to his admission he began to experience moderately severe frontal headaches. On several occasions he had chilly sensations associated with fever. There were also some pains described as aching in type in his elbow and knee joints. There was no history of previous serum therapy. His past history and family background were noncontributory.

Physical examination revealed a moderately ill white man in no great distress. The temperature, pulse rate and respiration rate were 102 F., 86 and 20, respectively. Aside from slight enlargement of the lymph nodes in the anterior cervical chain, the remainder of the physical examination revealed no abnormalities.

Laboratory findings on admission were as follows: Reaction to the Kahn test (qualitative) was doubtful. Urinalysis revealed no abnormalities. A complete blood count showed 4,400,000 red cells, with a hemoglobin content of 15.5 Gm. per hundred cubic centimeters, and 10,200 white blood cells, with 15 per cent polymorphonuclear cells, 1 per cent eosinophils, 2 per cent monocytes and 82 per cent lymphocytes. Many of the lymphocytes were atypical in form and conformed to the description of cells seen in infectious mononucleosis.

In view of the poorly defined clinical picture and because of the white blood cell count and the differential blood count, a tentative diagnosis of infectious mononucleosis was made. Thirty-six hours after the patient's admission to the hospital blood drawn for a heterophile antibody test was positive in a dilution of 1 : 1,792. (Unfortunately, since the specimen had to be sent to another laboratory the report was obtained several days after the patient died.)

The course in the hospital was as follows: On September 22 the patient complained of increasing headache. Examination revealed a moderate degree of nuchal rigidity, but that otherwise his condition remained unchanged. A lumbar puncture was productive of clear fluid under normal pressure, with a white blood cell count of 9,700, of which 94 per cent were lymphocytes and 6 per cent were polymorphonuclear leukocytes. The sugar content was normal and the protein increased. Smear and culture of the fluid proved to be sterile.

On September 23 a succession of neurologic symptoms and signs rapidly developed. He complained of tingling and numbness in his hands and feet, weakness in all four extremities and some difficulty in swallowing. His temperature, pulse and respirations were normal. The patient remained clear in sensorium although somewhat apprehensive. Examination revealed (1) complete paralysis of the right side of the face of a peripheral type; (2) moderate depression of the gag reflex; (3) hypesthesia in both hands and feet corresponding to the sensory components of the peripheral nerves, a symptom definitely against the diagnosis of poliomyelitis; (4) weakness of the muscles of the shoulder girdle, and (5) flaccid paralysis of the

muscle groups of all four extremities, with absence of the triceps, biceps, patellar and ankle reflexes. Respiratory movements were accomplished without difficulty. There was no involvement of the thoracic and abdominal musculature or of the rectal and urinary sphincters. Fibrillary tremors were not demonstrable. The picture was one of an extensive, rapidly progressing peripheral neuropathy associated with meningoencephalitis.

Because of the alarming progression of signs, the patient was transferred to a hospital equipped with a mechanical respirator. Despite the absence of the typical albuminocytologic dissociation in the spinal fluid, the diagnosis on transfer was "infectious neuritis of the Guillain-Barré type."

On September 24 the patient showed progressive deterioration, with complete quadriplegia, dysphagia and paralysis of the diaphragm. He was placed in the respirator, and other supportive measures were instituted. The laboratory findings at this time were as follows: A blood count showed 4,600,000 red blood cells, with a hemoglobin content of 15 Gm. per hundred cubic centimeters, and 13,300 white blood cells, with 21 per cent polymorphonuclear cells and 79 per cent lymphocytes. The spinal fluid contained 36,000 white blood cells, with 2 per cent polymorphonuclear cells and 98 per cent lymphocytes, and a total protein content of 81 mg. per hundred cubic centimeters. Culture of the fluid was sterile, and a culture of the blood also showed no growth.

On September 25, despite treatment, the patient died in respiratory failure.

Autopsy.—Three hours after death autopsy was performed. The positive findings were listed as follows:[2]

Lungs: The lungs showed early patchy bronchopneumonia, most pronounced in the lower lobes.

Cardiovascular System: Aortic atheroma was evidenced in the cardiovascular system, which was otherwise normal.

Spleen: Vascular changes and enlargement such as is described in association with infectious mononucleosis (see explanation) were seen in the spleen.

Liver: Examination of the liver revealed interstitial hepatitis associated with vascular changes comparable with those seen in the spleen.

Bone Marrow: There were reactive changes in the bone marrow compatible with a diagnosis of infectious mononucleosis.

Brain: In the brain there was increased vascular reaction of the pia-arachnoid. There were petechial and small perivascular hemorrhages throughout the cerebral cortex. In the cerebellum there occurred moderate degeneration of the cells of Purkinje. In the spinal cord degeneration and atrophy of the anterior horn cells were occasionally noted. Microscopic examination of certain peripheral nerves revealed interstitial fibrosis and cellular infiltrations.

The remainder of the organs were normal. The changes in the nervous system were comparable to those seen in the Guillain-Barré syndrome.

Changes described in the spleen and liver were considered pathognomonic for infectious mononucleosis, according to criteria set down by Smith and Custer.[3]

CASE 2.[4]—A 21 year old white man was admitted to a station hospital on Nov. 28, 1945, complaining of chilly sensations, headache and weakness. His family

2. Both in the first and second cases the pathologic reports are limited to summaries. Full descriptions of the gross and microscopic changes will appear in another paper concerning the pathologic aspects of infectious mononucleosis.

3. Smith, E. B., and Custer, R. P.: Rupture of the Spleen in Infectious Mononucleosis: A Clinicopathologic Report of Seven Cases, Blood **1**:317 (July) 1946.

4. This case was abstracted from the files of the Army Institute of Pathology, Colonel J. E. Ash, Medical Corps, Director.

and past history were noncontributory. Except for moderate fever and redness of the throat, the physical examination revealed nothing abnormal. With nonspecific therapy, he recovered sufficiently to be discharged from the hospital on December 1. Culture of material from the throat at this time did not reveal Corynebacterium diphtheriae.

On December 16 the patient was readmitted to the same hospital because of an increasingly severe sore throat. He also complained of soreness and weakness of the muscles of the lower extremities. Physical examination at this time revealed the following picture: The throat was moderately reddened. The cervical lymph nodes were enlarged. In the chest the lungs were clear, but over the cardiac apex a loud, blowing systolic murmur was heard. The blood pressure was normal. Examination of the abdomen revealed no abnormalities. The muscles of the calves and thighs were tender to pressure. The muscles of all four extremities exhibited weakness. The deep reflexes were absent. No sensory changes could be demonstrated.

Laboratory examinations gave the following results: In the spinal fluid the sugar content was 50 mg., the total protein content 74 mg. and the chloride content 627 mg. per hundred cubic centimeters. The white blood cell count was 8,000 (no differential count was done). A culture and smear of material from the throat failed to reveal C. diphtheriae. The electrocardiogram was normal.

The patient was given 40,000 units of diphtheria antitoxin and adequate doses of penicillin. During the next twenty-four hours he became progressively weaker. Transfer to another hospital was effected on December 19.

Physical examination on his arrival at the hospital revealed an acutely ill white man. The palate and pharynx at this time were diffusely reddened, edematous and covered with patches of white exudate. The cervical nodes were enlarged. In the thoracic wall there were absence of intercostal action of the upper two thirds and weakness in the lower third. Movements of the diaphragm were accomplished without apparent restriction. The lungs, heart and abdominal organs seemed normal. Aside from the intercostal difficulty, the involvement of the nervous system consisted in weakness of the muscles of the upper extremities, definite paralysis of the muscles of the lower extremities of the flaccid type and absence of the deep reflexes. Despite complaints of transient paresthesias of the hands and feet, objective sensory changes could not be demonstrated.

On December 19 the following laboratory data were obtained: Smear and culture were negative for C. diphtheriae. A complete blood count showed 4,740,000 red blood cells, with a hemoglobin content of 90 per cent, and 9,900 white blood cells, with 56 per cent neutrophils, 39 per cent lymphocytes and 5 per cent monocytes. The urine was normal, and a blood culture showed no growth.

In the next twenty-four hours the patient went rapidly downhill, and he died in respiratory failure on December 20. The clinical diagnosis was infectious polyneuritis of Guillain-Barré.

Pathologic Diagnosis.—Briefly, the pathologic diagnosis was as follows: Conditions in the respiratory system were acute nasopharyngitis, acute laryngitis, acute tracheobronchitis and atalectasis of the lower lobes of both lungs and the middle lobe of the right lung; in the spleen and hemopoietic tissues, acute splenitis, acute passive congestion of the spleen and acute lymphadenitis of the cervical, tracheobronchial, bronchopulmonary and abdominal lymph nodes; in the liver, acute passive congestion and in the nervous system, infectious polyneuritis (Guillain-Barré syndrome).

The neuropathologic diagnosis was based on the finding of: (1) congestion of the leptomeninges; (2) increased congestion, petechial hemorrhages and occasional

degeneration of the ganglion cells throughout the cerebrum, pons and medulla; (3) inflammation of the leptomeninges, small hemorrhages and occasional degeneration of the ganglion cells in the posterior horns at several levels of the spinal cord, and (4) perivascular cellular infiltrations of the sheaths and swelling of the myelin sheaths of several peripheral nerves.

In summary of the second case, the diagnosis of Guillain-Barré syndrome was made from the clinical picture. This diagnosis was substantiated by the autopsy. The diagnosis of infectious mononucleosis was made by the pathologist after detailed examination of the spleen and lymph nodes. Unfortunately, a heterophile antibody test was not done to substantiate the diagnosis.

Virus studies were accomplished by the injection of material from the brain and spinal cord into mice and guinea pigs. No virus could be isolated.

COMMENT

The etiology of infectious mononucleosis remains unknown. The disease may occur sporadically or appear in small epidemics. Characteristically, it affects children and young adults. The manifestations are varied, but in general they fall into three main categories. There are: (1) the glandular or Pfeiffer type, with either slowly or rapidly developing generalized lymphadenitis and splenomegaly; (2) the anginose or pharyngeal variety, resembling those of acute ulcerative tonsillitis, and (3) the febrile type, often treated as indicative of fever of undetermined origin. Many other cases cannot be classified so simply. In reviewing the subject, Bernstein [5] has pointed out the common occurrence of such symptom complexes as hepatitis with or without icterus, cutaneous eruptions of various kinds, hemorrhagic phenomena and neurologic concomitants. The prognosis is almost always favorable for complete recovery. The diagnosis may be suggested by the white blood cell count and blood smears exhibiting either a relative or absolute predominance of mononuclear cells with atypical lymphocytes. In most cases the diagnosis can be substantiated by the finding of a positive heterophile antibody reaction of high titer. The treatment is purely symptomatic.

Known facts about the pathologic process in infectious mononucleosis are meager because of the rarity of death from this disease. Most of the information, based on biopsies of lymph nodes and punctures of the bone marrow, revealed infiltration of mononuclear cells.[5] In a case in which death was due to rupture of the spleen Ziegler [6] noted infiltration of mononuclear cells in many organs and tissues, presenting a picture of a generalized infection with specific localizations. Lesions of the spleen and liver as described by Smith and Custer [3] are considered characteristic of infectious mononucleosis. In the spleen

5. Bernstein, A.: Infectious Mononucleosis, Medicine **19**:85 (Feb.) 1940.

6. Ziegler, E. E.: Infectious Mononucleosis: Report of a Fatal Case with Autopsy, Arch. Path. **37**:196 (March) 1944.

there occurs moderate cellular infiltration of the capsule and considerable hyperplasia of the red pulp. Typical vascular changes are seen in the adventitia of the trabecular arteries, in which infiltrations of mononuclear cells are encountered. The subintima of the trabecular veins present a similar situation. Vessels in the portal areas of the liver show changes like those in the spleen. These findings were present in the 2 cases reported here.

The infective agent may attack any organ or system. Involvement of the nervous system is not uncommon in infectious mononucleosis. The most frequent manifestation is lymphocytic meningitis. Reports of manifestation with this case have been made by Epstein and Dameshek,[7] Gsell,[8] Huber,[9] Thelander and Shaw [10] and Coogan and his associates.[11] The meningitis may occur at any time during the course of the disease. The symptoms of meningeal involvement may be absent, and the complication may be found on routine lumbar puncture. In others the usual picture of meningismus is present during the course of the disease. The spinal fluid is not characteristic except for the predominance of lymphocytes in the smear. The protein content may be normal or elevated; the sugar and chloride levels are normal, and the cultures are sterile.

The involvement of the nervous system may be so extensive as to produce symptoms of encephalopathy in addition to those of meningitis. A case with cerebellar symptoms was reported by Landes and others.[12] Patients presenting unilateral ptosis,[7] palsy of the peripheral facial nerves [8] and weakness of the pharyngeal muscles (case 1) have either direct nuclear involvement or disease of the nerve distal to the nucleus. Aside from the focal signs, patients may exhibit more general indications of cerebral disease, such as diplopia, delirium, lethargy and impaired memory.

A third type of neurologic disorder found on occasion is peripheral neuropathy. The cases reported previously illustrate widespread polyneuritis. Disease of the peripheral nerves in infectious mononucleosis

7. Epstein, S. H., and Dameshek, W.: Involvement of the Central Nervous System in a Case of Glandular Fever, New England J. Med. **205**:1238 (Dec. 24) 1931.

8. Gsell, O.: Serous Meningitis in Pfeiffer's Glandular Fever (Infectious Mononucleosis), Deutsche med. Wchnschr. **63**:1759 (Nov. 19) 1937.

9. Huber, W.: Contribution to the Problem of Serous Meningitis in Pfeiffer's Glandular Fever, Schweiz. med. Wchnschr. **68**:892 (July 23) 1938.

10. Thelander, H. E., and Shaw, E. B.: Infectious Mononucleosis with Special Reference to Cerebral Complications, Am. J. Dis. Child. **61**:1131 (June) 1941.

11. Coogan, T. J.; Martinson, D. L., and Matthews, W. H.: Neurological Symptoms of Infectious Mononucleosis, Illinois M. J. **87**:296 (June) 1945.

12. Landes, R.; Reich, J. P., and Perlow, S.: Central Nervous System Manifestations of Infectious Mononucleosis: Report of a Case, J. A. M. A. **116**:2482 (May 31) 1941.

has been reported by Zohman and Silverman [13] and by Coogan and others.[11] Recovery was the rule, in contrast to the residuals usually found in the wake of acute anterior poliomyelitis in which the disease attacks the spinal cord.

Infectious mononucleosis with neurologic complications presents problems in differential diagnosis. When lymphocytic meningitis is present, abortive poliomyelitis, tuberculous meningitis, benign lymphocytic choriomeningitis, "serous" meningitis and the meningitis that may accompany the infectious exanthems must be ruled out. However, with peripheral polyneuritis the problem is more difficult. More common causes of meningoencephalitic neuropathies to be considered are acute paralytic poliomyelitis, polyneuritis of toxic, metabolic or infectious origin and the Guillain-Barré syndrome.

In the cases presented it is of interest to note the striking resemblance of the neurologic signs to those in patients with the Guillain-Barré syndrome as described by McDonald and Taylor [14] and Lewey.[15] From the review of Lewey's article the impression is gained that the Guillain-Barré symptom complex is actually a multitude of diseases having a common denominator in the albuminocytologic dissociation of the spinal fluid. This fact is borne out by the recent report of cases of polyneuronitis occurring as a sequela of diphtheria [16] and as a neurologic complication of infectious mononucleosis (case by Landes and others and present cases).

From the standpoint of pathologic change, the nervous system in infectious polyneuritis usually exhibits congestion of the meninges, cerebrum and spinal cord. However, more pronounced are the changes in the peripheral nerves, in which edema of the nerve bundles, congestion, focal cellular infiltrations and swelling and beading of the myelin sheaths may be seen.[1] In addition it must be remembered that the toxic or infectious agent producing the nervous changes may also attack the viscera. Sabin and Aring [17] recorded such involvement in patients dying from the Guillain-Barré syndrome.

The evidence presented indicates the necessity for viewing the Guillain-Barré syndrome as a generalized disease rather than as one

13. Zohman, B. L., and Silverman, E. G.: Infectious Mononucleosis and Encephalomyelitis, Ann. Int. Med. **16**:1233 (June) 1942.

14. Taylor, E. W., and McDonald, C. A.: The Syndrome of Polyneuritis with Facial Diplegia, Arch. Neurol. & Psychiat. **27**:79 (Jan.) 1932.

15. Lewey, F. H.: What Is the Guillain-Barré Syndrome? J. Pediat. **26**:165 (Feb.) 1945.

16. Delp, M. H.; Sutherland, G. P., and Hashinger, E. H.: Post-Diphtheritic Polyneuritis: A Report of Five Cases with Albumino-Cytologic Dissociation Simulating the Guillain-Barré Syndrome, Ann. Int. Med. **24**:618 (April) 1946.

17. Sabin, A. B., and Aring, C. D.: Visceral Lesions in Infectious Polyneuritis, Am. J. Path. **17**:469 (July) 1941.

limited to the nervous system. Infectious mononucleosis must be considered as a possible factor in the differential diagnosis of infectious neuronitis. In addition, when symptoms or signs of peripheral neuritis do arise in the course of infectious mononucleosis, one must be aware of the danger of paralysis of the respiratory system and death.

SUMMARY

1. Neurologic symptoms and symptom complexes in infectious mononucleosis have been briefly discussed.

2. In evidence that the Guillain-Barré syndrome may occur during the course of infectious mononucleosis, 2 cases are presented. Respiratory failure was responsible for the fatal outcomes in both cases. The essential pathologic findings are recorded.

3. The Guillain-Barré syndrome is the neurologic manifestation of many diseases of different origin.

4. Infectious mononucleosis must be considered in the differential diagnosis of infectious neuronitis.

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ANALYSIS OF A FOUR YEAR EPIDEMIC OF MUMPS

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AT FORT BENNING, GA., in the winter of 1941 there appeared an unusual increase in the number of cases of mumps, which reached a peak for that season of 49 new cases in the month of April 1942. There followed a cyclic rise and fall in the number of cases in the next three years, but the incidence never returned to the corresponding seasonal level at which it had been prior to 1941. The apex of the epidemic was reached in March 1944, when the maximum of 289 new patients were admitted during the month. Over the whole four year period a total of 2,500 patients were admitted. The seasonal distribution of the cases from 1942 through 1944 is shown in figure 1. A considerable proportion of these patients were admitted from the Reception Center, and during the last two years practically 90 per cent of the patients were from this center or its associated training schools. With these facts in mind, this might be considered as an "endemic epidemic," with the endemic focus being the Reception Center. Because of the duration of this epidemic, or series of epidemics as some may prefer to call it, it was thought desirable to analyze the data from these 2,500 cases in a search for any new clinical or epidemiologic facts that might be present.

The 2,500 cases were distributed through the four years as follows: 254 in 1942; 415 in 1943; 995 in 1944, and 836 in 1945. The data on each consecutive case in 1942 were recorded on a large analytic chart. The data from the first 100 consecutive cases of 1943 were likewise recorded. Thereafter charting was done only for cases with some unusual manifestation, although each clinical record was reviewed thoroughly. The majority of the statistical deductions are based on these three groups, with a total of 1,664 cases. For administrative reasons the charts of the 1945 group were not available, and the data used to represent these 836 cases were secured from the registrar's official statistics and from analytic data obtained from a report by Holden, Eagles and Stevens[1] of 100 consecutive admissions during the height of the 1945 peak of this epidemic.

1. Holden, E. M.; Eagles, A. Y., and Stevens, J. E., Jr.: Mumps Involvement of the Central Nervous System, J. A. M. A. **131**:382 (June 1) 1946.

EPIDEMIOLOGY

Table 1 summarizes the main epidemiologic findings. The average age of the patients of the whole four year period was 24.79 years. The range of the ages was from 18 to 54 years. The average age for each year, however, shows a steady decline from 27.83 years in 1942 to 22.27 in 1945. It is interesting to note the relationship of the 1943 and 1944 age averages and the accompanying proportion of white and Negro patients. There is almost a complete reversal of the ratio of white to Negro patients in the two years, but the ages remained the same. From the race ratio it is seen also that with the exception of 1943 there was a steady increase in the proportion of Negroes admitted from 1942 through 1945. All of the factors influencing this trend are

TABLE 1.—*Epidemiologic Data*

Years	1942	1943	1944	1945	Total Number or Average
Total number of patients	254	415	905	836†	2,500
Number of cases tabulated	254	185	306	100*	845
Average age	27.83	24.52	24.53	22.27*	24.79
Race ratio (white/Negro)	63/37	90/10	18.5/81.5	8/92*	45/55
Average months of service	13.06	10.83	8.84	5.22*	9.49
Number outside "South"	21.56%	54.62%	13.68%	.....	29.95%
Epididymo-orchitis	21.26%	24.33%	27.03%	24.28†	25.12
Clinical meningitis	14(5.5%)	8(1.9%)	22(2.2%)	(33%)*	44(2.6%)‡
Average total days in the hospital	14.38	18.75	.....	.....	.....
Days in the hospital (uncomplicated)	13.34	13.80	.....	.....	.....
Days in the hospital (complicated)	16.48	19.85	24.30	.....	.....

† Data obtained from the registrar's records.
* Holden, Eagles and Stevens' series.
‡ Cases in 1945 not included (total, 1,664).

not known, and since the distribution of the general population of the post during this interval is not known, no definite conclusions can be drawn.

McGuinness and Gall,[2] from their study in Camp McCoy, Wis., stated that mumps in epidemic form is unlikely to occur except among soldiers from rural areas of the South and Southwest. In an effort to confirm this, the patients from the "South" were separated and the number from elsewhere were tabulated in descending order according to the year and to their native states. The following states were arbitrarily considered as the "South": Virgina, North Carolina, South Carolina, Georgia, Florida, Tennessee, Mississippi, Alabama and Louisiana. In table 1 can be seen the distribution of cases outside of the South, which was as follows: 21.56 per cent in 1942, 54.62 per cent

2. McGuinness, A. C., and Gall, E. A.: Mumps at Army Camps in 1943, War Med. **5**:95 (Feb.) 1944.

in 1943 and 13.68 per cent in 1944. Thus the percentage as seen in 1943 would not uphold the aforementioned statement. Even with the inclusion of those from Texas, Oklahoma, Arkansas and Missouri as representing the Southwest, the percentage is still 35.6 per cent of all patients from elsewhere than the South and Southwest.

The duration of hospitalization for all patients seen in 1942 averaged 14.38 days. When differentiation is made between the simple forms of the disease and those with unusual manifestations, the duration in the "uncomplicated" cases averaged 13.34 days and in the compli-

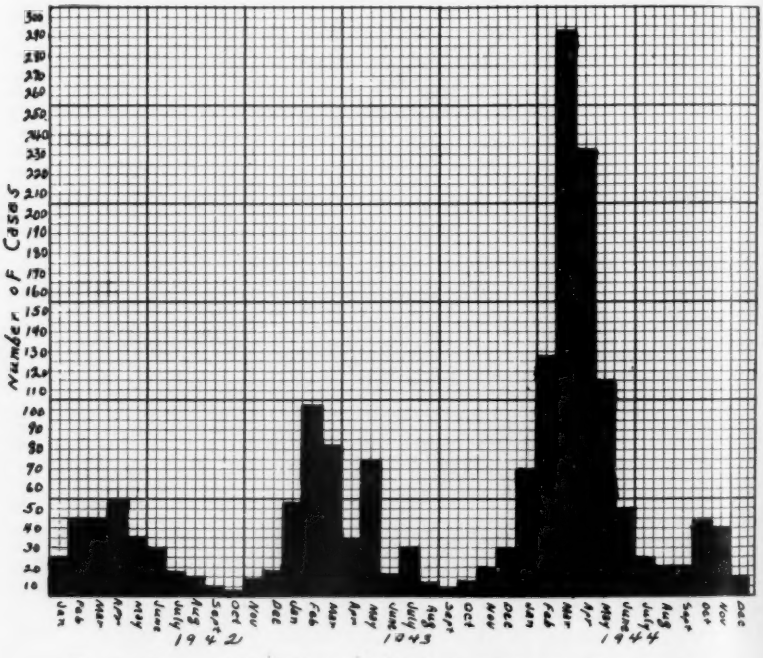

Fig. 1.—Seasonal distribution in epidemic of mumps over three years.

cated ones 16.48 days. Among the first 100 cases in 1943 the average for the uncomplicated attacks was found to be 13.80 days—probably no significant variation from that of 1942. However, in the complicated cases in 1943 and 1944 the disease was of progressively increasing duration, the average being 19.85 days in 1943 and 24.30 in 1945. Although there were several extraneous factors which might have affected these figures, the possibility of an increasing virulence of the infection is definitely suggested.

Similar to the occurrence in the age incidence, the duration of service at the time of the patient's admission to the hospital steadily

decreased throughout the four year period. In 1942 the average duration of service at the time of admission was 13.06 months, and by 1945 it had fallen to only 5.22 months.

The seasonal distribution fell into the usually expected pattern and can be seen for the years 1942 to 1944 in figure 1.

CLINICAL COURSE

The general course of the disease can be described as being typical of that usually seen in cases of mumps in adults. The patients were admitted from outlying dispensaries by way of "sick call" to the hospital, where they were isolated. The average number of days of illness before hospitalization was only 1.53; however, it varied from none to 14 days. Patients waiting 10 to 14 days after the onset of salivary involvement before seeking hospitalization were usually found to have orchitis and little if any salivary enlargement. They usually gave one of the following histories: (1) they had had little salivary swelling and didn't know what it was; (2) they had applied to "sick call" and the doctor failed to make the diagnosis, or (3) they had requested permission of the sergeant to report to "sick call' and had been refused. Usually, however, the presenting complaints were of swollen and painful jaws, headache and a low to moderate degree of fever.

No reliable data were obtained in relation to the duration of rest in bed, but general observation seemed to confirm previous experiments showing no relationship with the incidence of orchitis. Rest in bed with bathroom privileges was the general rule for any febrile episode and until the greater part of the salivary swelling had disappeared. After that it was practically impossible to impose rest in bed on the majority of the patients.

The incidence and distribution of the salivary glands involved are shown in table 2. The figures correspond fairly closely with those of McGuinness and Gall [2] and Haerem.[3] Following the example of the first two authors, the total days and "units" of fever were tabulated for each of the various manifestations of the disease. The unit is considered as 1 degree (F.) of temperature above normal for each day. By this method one gets another indication of the severity and toxicity of the disease. For example, it reveals the difference between one patient who had a temperature of 100 F. for three days and another who had fever for the same number of days, but with a temperature of up to 103 F. each day. The units would be 2 per day, a total of 6, for the first patient, while for the second patient there would be 5 units per day, or a total of 15. When two manifestations occurred

3. Haerem, A. T.: Observations on Mumps in Soldiers, Mil. Surgeon **97**:33 (July) 1945.

simultaneously, the fever was tabulated to the credit of the more severe syndrome. In table 3 is seen the distribution of fever in the involvement of the salivary glands over the three year period. The average number of days of fever in these so-called uncomplicated cases is 2.11, and the average number of units is 4.99. However, it should be noted that, while the average number of days of fever varied little from year to year, there was a definite increase in the average number of units of fever in these "uncomplicated cases"—from 3.55 in 1942 to 7.14 in 1944. The range of days extends from 0 to 9, while that of the units

TABLE 2.—*Involvement of the Salivary Glands*

Year (Number of Tabulated Cases in Parentheses)	1942 (254)		1943 (185)		1944 (306)		1945 (100)		Total (845)	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Parotid, bilateral	134	52.75	125	67.57	203	66.3	68	68	530	62.7
Right parotid	46	18.11	27	14.59	52	16.9	16	16	141	16.7
Left parotid	71	27.95	30	16.22	41	13.4	16	16	158	18.7
Submaxillary, bilateral	6	2.36	15	8.05	17	5.6	..	..	38	5.1
Right submaxillary	11	4.33	4	2.16	13	4.2	..	..	28	3.6
Left submaxillary	12	4.72	10	5.42	13	4.2	..	..	35	4.7
Parotid and submaxillary	22	8.66	23	12.43	39	12.7	..	..	84	11.3
Submaxillary only	3	1.18	3	1.62	4	1.4	..	..	10	1.3
Without involvement of the salivary glands	0	0	0	0	6*	2.0	..	..	..	...

* Of these, 4 had epididymo-orchitis and 2 had meningoencephalitis.

TABLE 3.—*Duration and Degree of Fever in Involvement of the Salivary Glands*

Year	1942		1943		1944		Total	
Number on which data were obtained	231		156		245		632	
"Uncomplicated" Fever	Average	Range	Average	Range	Average	Range	Average	Range
Days	1.9	0 to 8	2.25	0 to 9	2.20	0 to 7	2.11	0 to 9
Units	3.55	0 to 23	4.28	0 to 11	7.14	0 to 18	4.99	0 to 23
Total Fever								
Days	3.1	0 to 11	....	.....	....	.....	....	.....
Units	7.02	0 to 36	....	.....	....	.....	....	.....

extends from 0 to 23. The complete data in relation to fever are unavailable except for the year 1942, when the total number of days of fever was 3.1 and the number of units 7.02, with a corresponding total range of 0 to 11 days and 0 to 36 units.

EPIDIDYMO-ORCHITIS

There were 425 instances of epididymo-orchitis in the 1,664 cases of the first three years, which were individually reviewed; there were 203 more instances of epididymo-orchitis in the 1945 series of 836 cases, which could not be reviewed. This gives a total of 628 cases of orchitis out of the series of 2,500, making an incidence of 25.12 per cent. Because a general impression had been obtained of an irregular cyclic

variation in the occurrence of orchitis, a thorough check was made of the first 400 patients in this series admitted to the hospital. No significant grouping of the cases of orchitis was found. The distribution of the cases can be seen from table 4 and confirms previous reports as to the various incidences. However, the yearly averages show an increasing incidence of epididymo-orchitis from 21.26 per cent in 1942 to 27.03 per cent in 1944, again suggesting an increasing virulence of the virus as the epidemic progressed. The day of onset of orchitis in relation to that of parotitis remained fairly constant, with an average of 4.5 days after salivary swelling began. The extremes are remarkable, however, ranging from 14 days before salivary involvement to 25 days after. Patients in whom the complication developed after three weeks

TABLE 4.—*Distribution of Cases of Epididymo-Orchitis*

	1942		1943		1944		1945	Total	
Year									
Total number of cases	254		415		995		836	2,500	
Number of cases of orchitis (per cent).	54 (21.26%)		102 (24.33%)		269 (27.03%)		203 (24.28%)	628 (25.12%)*	
Distribution of orchitis	Number	Per Cent	Number	Per Cent	Number	Per Cent	...	Number	Per Cent
Right side	24	44.4	55	53.9	120	44.9	...	199	46.8
Left side	25	26.3	32	31.4	103	38.2	...	165	38.8
Bilateral	5	9.3	15	14.7	43	15.9	...	63	14.8
Undesignated	0	....	0	....	3	1.1	...	...	....
Time of onset after parotitis									
Average	3.55 days		5.3 days		4.6 days			4.5 days	
Range	14 days before to 11 after		0 to 20 days after		0 to 25 days after			14 days before to 25 days after	
Fever	Days	Units	Days	Units	Days	Units		Days	Units
Average	3.81	12.9	3.36	11.6	3.8	13.3	...	3.66	12.6
Range	0 to 7	0 to 34	1 to 9	1 to 38	0 to 9	0 to 42	...	0 to 9	0 to 42
Miscellaneous	5 cases of orchitis without parotitis Only 2 cases of total number operated on								

* Four hundred and twenty-five instances of orchitis occurred in the first three years in a total of 1,664 patients.

were, as pointed out by McGuinness,[2] practically afebrile, but no essential differences were noted in those with an earlier onset. The average duration of fever due to the manifestations of orchitis was 3.66 days, with a range of 0 to 9 days, and the average degree was 12.59 units, with a range of 0 to 42. Out of 995 cases in 1944 there were 5 instances of orchitis without involvement of the salivary glands and in 1 of these the patient had an associated meningoencephalitis. One similar case,[4] not included in this series, was reported because of meningeal signs present on the patient's admission to the hospital and the subsequent development of epididymo-orchitis. The cause in this case was definitely established by a positive reaction to complement fixation tests for mumps.

4. Eagles, A. Y.: An Unusual Case of Mumps Without Parotitis, Bull. U. S. Army M. Dept. **5**:598 (May) 1946.

Out of the series of 425 cases of orchitis reviewed, in 63 the condition was bilateral. From the entire series of 628 patients, only 2 underwent the surgical treatment of incision of the tunica albuginea, as advised by Wesselhoeft and Vose.[5] Both of these had bilateral orchitis, but the operation was bilateral in only 1. Pain subsided promptly in each case, although fever persisted for twenty-four hours following operation. In the patient with a unilateral operation the incision healed in six weeks, while in the patient with the bilateral operation it healed in four weeks. Follow-up was available on only 1—a white enlisted man of the medical department, stationed at the hospital. One and a half years later, when questioned, he reported a softness present in the testicle operated on, with mild residual soreness. He also claimed some diminution of libido, although he admitted it might be psychogenic in origin. On several occasions surgical treatment was advised for patients with extremely swollen testicles, after a thorough explanation of the reason, methods and results to be expected therefrom. Most of them refused the treatment. Symptomatic therapy of orchitis consisted of strict rest in bed with an adhesive bridge for support, application of an ice bag locally and liberal use of acetylsalicylic acid and small doses of codeine as necessary. In extreme instances of high fever, nausea and vomiting, administration of parenteral fluids became necessary, as it was not uncommon to observe temperatures of 105 F. or more with this episode.

From the report of Gellis and others[6] on two groups of patients in the 1944 series of this epidemic, it is seen that the use of gamma globulin, when available, is worth while in the prevention of orchitis. In 51 patients treated with 20 cc. of gamma globulin made from mumps convalescent serum, orchitis occurred in 7.8 per cent, while in the controls it occurred in 27.4 per cent. In 67 patients treated with 50 cc. of gamma globulin from pooled normal human plasma the percentage in which orchitis occurred was 20.9, compared with 26.8 per cent for the controls. The first group received the equivalent of 400 cc. of convalescent serum globulin or the equivalent (in antibody content) of 4,000 cc. of normal pooled plasma. Despite these encouraging results, the practical application awaits the development of an adequate supply of the fractionated protein.

PRESTERNAL EDEMA

Gellis and Peters[7] in the early part of 1944 carefully examined 500 patients in this same epidemic and from their personal records found that

5. Wesselhoeft, C., and Vose, S.: Surgical Treatment of Severe Orchitis in Mumps, New England J. Med. **227**:277 (Aug. 3) 1942.

6. Gellis, S. S.; McGuinness, A. C., and Peters, M.: A Study of Prevention of Mumps Orchitis by Gamma Globulin, Am. J. M. Sc. **210**:661 (Nov.) 1945.

7. Gellis, S. S., and Peters, M.: Mumps with Presternal Edema, Bull. Johns Hopkins Hosp. **75**:241 (Oct.) 1944.

presternal edema occurred in 30, or 6 per cent of their whole group. This syndrome is a symmetric painless pitting edema of the soft tissues overlying the sternum, associated with swelling of salivary glands due to mumps. In by far the greatest number of cases the condition is associated with submaxillary glandular involvement. The edema persists for five days on the average. The onset usually occurs five to six days after the appearance of the glandular swelling. The distribution and pitting nature of the edema may be seen from the accompanying photographs of a patient in whom the condition was of average severity.

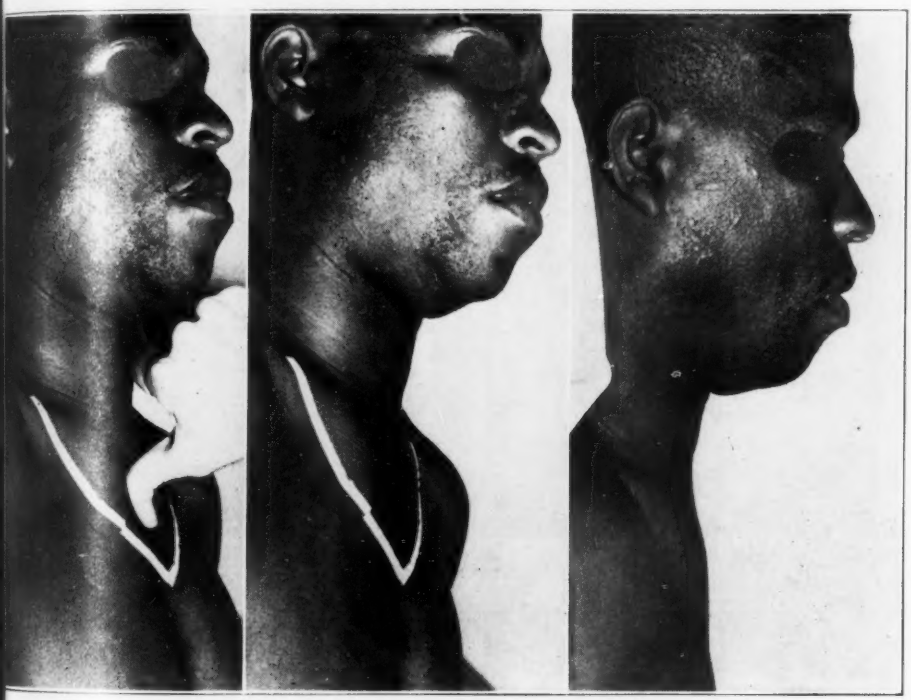

Fig. 2.—Patient with presternal edema of average severity. Note distribution and pitting. (Photo by U. S. Army Signal Corps.)

Although dangerous symptoms are not usually seen with this syndrome, on rare occasions a serious danger of tracheal obstruction from the increased pressure within the tissues of the neck may be observed. The cause is thought to be obstruction to lymphatic drainage by the salivary glands concerned.

In the review of the 1,664 cases occurring during the entire period 1942 through 1944, only 21 instances of presternal edema were found

recorded, giving an incidence of 1.2 per cent. This closely corresponds to the observations of Haerem,[8] who found an incidence of 1 per cent in his series of 1,470 cases. The variation in these figures from those of Gellis and Peters undoubtedly represents the difference between careful personal observations and the collection of statistics from a review of clinical records.

IMMUNITY

The data from the cases in 1942 and 1943 reveal that 30 of 439 patients examined gave a history of previous infection. Of these, only 18 specified that their previous infection had been unilateral. Thus there seems to be no foundation for the general impression that the immunity gained from unilateral parotitis is not as permanent as that from bilateral salivary involvement. Three cases of recurrent parotitis were seen, the disease each time being typical of epidemic parotitis in its clinical picture and course. There was one relapse of orchitis, with a repetition of fever, swelling and pain on the same side after seven days' freedom from all symptoms or signs.

MISCELLANEOUS ENTITIES

It may seem surprising that pancreatitis is relegated to the class of miscellaneous manifestations in mumps. Yet out of 1,664 cases there were only 3 in which the symptoms and signs of pancreatitis could be observed clinically.

Considerable literature has appeared recently emphasizing the occurrence of myocarditis in mumps, although in many cases it is detectable only by electrocardiographic evidence. Only 3 cases were found in the records of the whole series in which myocardial involvement could be suspected clinically. In 1 there was sinus bradycardia without symptoms, and in 2 there was tachycardia without symptoms or abnormal electrocardiographic findings. However, Peters and Penner[8] investigated some of the cases occurring in 1945 with routine electrocardiographic studies and found that the incidence was no higher than could be expected in any other acute infectious disease. The electrocardiographic changes were not specific for mumps.

There were 6 out of the 995 cases in 1944 in which there was some ocular involvement. The diagnoses were keratitis (2), conjunctivitis (3) and conjunctivitis and iritis (1). Treatment was given with sodium sulfathiazole in the form of eye drops or ointment, with application of pressure bandages when corneal ulceration was present.

There were only 8 cases in which bronchitis could be definitely associated with mumps. In these the condition varied in severity, but none of the patients showed any roentgenographic signs of abnormality in their chests.

8. Peters, M., and Penner, S.: Personal communication to the author.

From the previously reported results in 100 cases studied from the 1945 series,[1] no correlation was expected in this series between the white blood cell count and any of the manifestations of mumps. The average white blood cell count in all cases in 1942 was 6,780, while in 1944 in the "complicated" cases only it was 6,442. The average differential count in all cases in 1942 was 55.6 polymorphonuclear cells and 38.6 lymphocytes, and in the 1944 complicated cases alone the ratio was 55.8 to 39.6.

No adequate study was made of the relationship of serum amylase content to the various manifestations of the disease. A general impression was obtained of the highest values for serum amylase being associated with the height of salivary swelling, similar to that found by Huerem.[8] In Bang and Bang's [9] series of cases of mumps, 60 per cent (230 of 371) of the patients with salivary involvement had an elevated urinary diastase content. However, of their 13 patients without salivary involvement (11 with meningitis and 2 with orchitis), 7 had an elevated urinary diastase value. This relationship should be worked out more thoroughly to determine the efficacy of the values for amylase content as an aid in the diagnosis of obscure forms of mumps, particularly in relation to pancreatitis.

MENINGOENCEPHALITIS

The term meningoencephalitis is used in accordance with the American consensus in respect to all cases of mumps in which there are signs either of primary meningeal irritation with considerable pleocytosis or of primary encephalitis with a paucity of cellular elements in the spinal fluid or any combination of the two. It also includes the latent group of cases in which there is pleocytosis with no objective clinical signs of involvement of the central nervous system. This is in contrast to the use of the term made by the Scandinavians, who make a distinction between meningitis and meningoencephalitis, limiting the latter term to the less commonly encountered cases with clinical signs of severe encephalitis as well as of primary meningeal irritation.[10] By making this distinction, they rightly point out the rarity of the occurrence, the more severe symptoms and signs and the increasing number of permanent sequelae seen in their "meningoencephalitic" group.

The diagnosis of clinical involvement of the central nervous system was made by the presence of the following specific symptoms and signs: severe headache, drowsiness, nausea or vomiting and stiff neck. The level of cellular abnormality of the spinal fluid was taken to be 10 cells

9. Bang, H. O., and Bang, J.: Involvement of the Central Nervous System in Mumps, Acta med. Scandinav. **113**:487 (April) 1943.

10. Levison, H., and Thordarson, O.: Mumps Meningitis and Meningo-Encephalitis, Acta med. Scandinav. **112**:312 (Oct.) 1942. Bang and Bang.[9]

or more per cubic millimeter. The data obtained are summarized in table 5. Among 1,664 cases reviewed from 1942 through 1944, there were 44 with signs of meningoencephalitis. Since no specific study was being made in this group, lumbar punctures were done only as a diagnostic or therapeutic procedure, although in some they were repeated as many as three times. A total of 26 patients had spinal punctures, and in 21 of these the fluid contained at least 10 cells or more per cubic millimeter, with the maximum reaching 570 cells per cubic millimeter. Thus the incidence of clinical (proved and suspected) meningoencephalitis was 2.6 per cent in the total number of cases reviewed, while the incidence actually proved by spinal puncture was 1.26 per cent. In only 1 case was there variation from the usual predominantly lymphocytic distribution of cells. Treatment with sulfadiazine failed to have any therapeutic effect on the patient involved.

TABLE 5.—*Meningoencephalitis (1942 to 1944)**

Year (total number of cases in parentheses)	1942 (254)	1943 (415)	1944 (995)	Total Average
Number clinically suspected	14	8	22	44 (2.6%)
Number on which spinal punctures were done	7	2	17	26
Number in which the spinal fluid contained 10 cells or above	5†	2†	14†	21 (1.26%)
Fever				
Days	3.75	5.5	4.25	4.5
Units	11.75	20.5	13.6	15.28

* The average time of onset following parotitis was 4.25 days, and the range was within one day before to more than eighteen days after.

† The range was 0 to 570, and in cases in which the content was less than 10 cells the numbers were 0, 0, 2, 4 and 7.

The average time of onset of signs of meningeal involvement was 4.25 days following the appearance of the salivary swelling. Of the 995 cases observed in 1944, there were 2 in which meningeal signs preceded the parotitis and 2 in which there was no involvement of salivary glands at all. These types have been reported in several instances in the American and Scandinavian literature, and I have encountered at least 4 cases of primary meningoencephalitis without salivary swelling in which there was the confirmatory evidence of positive reactions to complement fixation tests. Fever is practically always present with signs of meningoencephalitis—so often that when it is lacking the existence of that manifestation is usually doubted unless there is an accompanying pleocytosis.

The spinal fluid pressure was elevated in many of the patients in this series, and decided relief from the severe headache, nausea and vomiting usually was obtained when as much as 15 cc. of spinal fluid was removed. The fever continues to run its usual course, however, with no correlation with the number of punctures performed or the amount of pressure relieved.

No definite data were obtained on spinal fluid protein content in this large group, but in a previous experiment on the small 1945 group [1] there did seem to be a significant elevation of spinal fluid protein content in cases of both clinical and subclinical disease.

In the early part of 1945 Holden, Stevens and Eagles [1] attempted to determine the incidence of clinical and latent meningoencephalitis by doing spinal punctures routinely on the fourth day of the disease in a series of 100 patients admitted to the hospital consecutively during this same epidemic. Bang and Bang [9] described a similar though larger series of 458 cases, involving civilians of all ages seen in the University Clinic of Epidemic Diseases in Copenhagen, in which spinal punctures were done in 371, or 85 per cent. According to the authors, the patients,

TABLE 6.—*Comparative Tables of Meningitis*

	Before Adjustment			After Adjustment		
	Bang and Bang Series		Holden, Eagles and Stevens Series, Cases and per Cent	Bang and Bang Series		Holden, Eagles and Stevens Series, Cases and per Cent
Classes	Cases	Per Cent		Cases	Per Cent	
1. Mumps without meningitis	126	34	63	161	43.4	63
2. Mumps with meningitis	245*	66	37	210	56.6	37
3. Manifest	106	28.6	28	97	26.1	28
4. Latent	129	34.5	4	94	25.3	4
5. Meningism	10	2.7	5	19	5.1	5
Distribution of Cases of Meningitis						
	210 cases, 100%			37 cases, 100%		
Manifest	46.1			75.5		
Latent	44.7			10.8		
Meningism	9.0			13.5		

* Original figures containing class 5 cases.

although admitted to a hospital for the treatment of contagious diseases, were for the most part suffering from uncomplicated mumps on admission. They divided their cases into four principal groups and designated them as follows: (1) uncomplicated cases, (2) cases with manifest meningitis (clinical signs plus pleocytosis), (3) cases with latent meningitis (pleocytosis without clinical signs) and (4) cases with meningism (clinical signs without pleocytosis). An effort has been made to compare our results from the study of a military group with those from the group of civilians of all ages studied by Bang and Bang. With utilization of information given in both articles, the results from each series were adjusted to meet similar standards for comparison. The Scandinavian classification of the types of cases was used, but the indication of pleocytosis of 3 cells per cubic millimeter was adjusted to the American standard of 10 cells. The original and the corrected figures are shown in table 6.

The total number of cases of meningitis in the two series after correction is seen to be 210, or 57 per cent, for the series studied by Bang and Bang and 37 for the series of 100 cases studied by Holden, Eagles and Stevens. The numbers with manifest or clinical meningitis are found to correspond closely, with the figure for the former series being 26.1 per cent in comparison with the incidence for the latter series of 28 per cent. The number with meningism is practically the same after adjustment, being 5.1 and 5.0 per cent in the two series. The greatest discrepancy is found in the number with latent meningitis, which is 25.3 per cent in the Bang and Bang series and only 4 per cent in the other. In searching for the cause of this variation, it was discovered that Bang and Bang, in their eagerness to use only objective signs, had diagnosed manifest meningitis only in those cases in which there was definite cervical rigidity. By so doing they automatically included in the latent group all those patients with the other valid signs of involvement of the central nervous system and pleocytosis. This, then, partially accounts for the high number of patients with latent meningitis, who theoretically should have no symptoms or signs of involvement of the central nervous system. The exact incidence of the various types will probably never be determined until they are actually compared with uniform criteria for the various classes of such involvement. Despite the arguments against comparison of these two series of cases for statistical purposes the figures are strongly suggestive of certain conclusions. Sixty-one per cent of the patients in the Bang and Bang series were 14 years of age or less, and this seems to argue against Holtz's statement [11] that meningitis occurs more commonly among children than among adults. It also seems evident from the close correlation of the cases of clinical meningitis (with and without pleocytosis) that when there is alertness to the frequency of this manifestation it can be found in approximately equal numbers in civilian and military populations.

SUMMARY AND CONCLUSIONS

An epidemic of mumps in soldiers in which 2,500 patients were hospitalized, extending over a period of four years, was studied clinically and epidemiologically.

Mumps may be found to occur in epidemic form outside the South and Southwest whenever large groups of young nonimmune soldiers are involved.

The incidences of the various manifestations of mumps did not vary from those found in epidemics of the usual duration. In this prolonged

11. Holtz, K.: Mumpsmeningitis, Deutsche med. Wchnschr. **57**:536 (March 27) 1931.

epidemic, however, there did seem to be a progressive increase in virulence of the disease as the epidemic persisted. This was manifested by the increase in the units of fever with the salivary involvement, the increasing incidence of orchitis and the increasing number of days of hospitalization for those with involvement other than that of the salivary glands.

Of the 1,664 cases reviewed, epididymo-orchitis occurred in 25.54 per cent, clinical meningoencephalitis in 2.6 per cent and presternal edema in 1.2 per cent. Pancreatitis was seen in only 3 cases, questionable myocarditis in 3 and ocular infections in 6.

A comparison of reports of involvement of the central nervous system in separate epidemics in military and civilian personnel reveals that the clinical manifestations of meningoencephalitis are found in approximately the same numbers in each class of patients when this complication is specifically searched for.

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ALLERGIC LESIONS FOLLOWING THROMBOPHLEBITIS

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PATIENTS who have had thrombophlebitis and patients with varicose veins frequently have complications in the skin which have been given descriptive names such as stasis dermatitis or stasis ulcers, varicose dermatitis or varicose eczema, or postphlebitic ulcer. Despite the large incidence of stasis lesions in the legs in many patients who have varicose veins or who have had phlebitis, little is known of the underlying reasons for the development and persistence of these lesions other than that a stasis factor is present. It is customarily thought to be sufficient to say that the lesion is due to stasis.

Attention was focused on these lesions by the appearance of a large number of patients with postphlebitic and varicose ulcers who began coming to the clinic with dermatitis, severe pruritus and pain in a leg following the local use of sulfathiazole powder or ointment. The large number of such patients drew our attention to the susceptibility of the leg to sensitization or allergic reactions after the occurrence of phlebitis. We then began to observe that in patients who had had phlebitis localized allergic reactions often developed in the affected leg when no drug was used locally. For example, whenever a generalized allergic cutaneous reaction developed in a patient with a phlebitic leg, this leg would become involved first by urticaria or dermatitis and practically always was the part most affected. In several patients who were taking penicillin urticaria developed on the phlebitic leg and later on the rest of the body. Often an allergic reaction was present in the leg and nowhere else. In 1 patient who was allergic to a great many substances severe pruritus and dermatitis would at times develop on the extremity affected by phlebitis. At times this would be followed by generalized involvement of the rest of the body. If a patient who has had thrombophlebitis takes a warm bath, the involved leg may itch severely. One patient had to sit and scratch the leg after a bath. The patients often have severe itching in the affected leg when they are warm. When warm, the arteries are dilated, so that the blood is brought freely to the skin, but in legs in which there has been thrombosis of a large vein the blood cannot get out

From the Peripheral Vascular Section of the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

easily and there occurs a local accumulation of substances to which the patient may be allergic.

Thrombosis of a vein may result in the local accumulation or trapping of quantities of an allergen sufficient to cause a local clinical allergic reaction. In an extremity in which this happens, sensitization may occur more easily as the result of slower blood flow and edema and consequent increased time of contact as well as increased quantity of allergen locally. In some allergic conditions the circulatory component may be a minor one. In the leg in which phlebitis has occurred it may be the predominant or precipitating one without which a low grade allergy might not have come to the surface or to the point of clinical manifestation. The local accumulation of sensitizing substances due to congestion has also been used to explain involvement of the butterfly area in lupus erythematosus. The rich vascularity of the flush area of the face accentuates the reaction in patients with this condition.

The concept expressed is the reverse of that in what has been called vascular allergy, in which an allergy may be the cause of the vascular disease, as, for example, in periarteritis nodosa or thromboangiitis obliterans (Rich,[1] Naide[2] and Thompson[3]). In the group of patients under discussion here, the vascular diseases thrombophlebitis and phlebothrombosis create the situation whereby allergens are trapped to bring out a subclinical allergic state or to accentuate a preexisting allergic lesion.

The sequence of events that may occur after thrombophlebitis is illustrated in the accompanying table. As the result of venous congestion, which may be due to incompetent veins as well as to thrombophlebitis, there may occur a local increase in concentration of allergens. The concentration may be to the point of clinical allergic manifestation, and a so-called stasis dermatitis or eczema develops. If there is trauma, there will be a local outpouring of these allergens into the traumatized area. This was beautifully illustrated in Auer[4] in 1920, who demonstrated that gangrene of a rabbit's ear would occur if the rabbit were sensitized and the ear traumatized and then the sensitizing agent reinjected, whereas the untraumatized ear would remain completely unharmed. Furthermore, the local accumulation of allergens may result

1. Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, Bull. Johns Hopkins Hosp. **71**:123-140 (Sept.) 1942.

2. Naide, M.: The Causative Relationship of Dermatophytosis to Thromboangiitis Obliterans, Am. J. M. Sc. **202**:822-831 (Dec.) 1941.

3. Thompson, K. W.: Studies in the Relationship of Dermatophytosis to Ulceration and Gangrene of the Extremities, Yale J. Biol. & Med. **16**:665-853 (July) 1944.

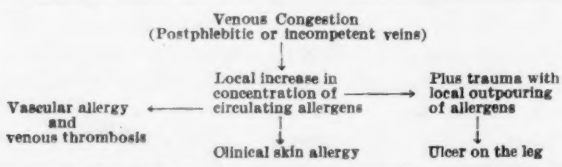
4. Auer, J.: Local Autoinoculation of Sensitized Organisms with Foreign Protein as Cause of Abnormal Reactions, J. Exper. Med. **32**:427 (Oct.) 1920.

in further local vascular reactions and thrombosis and thus create a vicious cycle, so that if additional venous thrombosis takes place further venous congestion is created, with increased tendency for accumulation of allergic substances.

It is of interest that we practically never see a postphlebitic or varicose ulcer on the foot. This is probably the result of the pumping action of the foot in walking, so that stasis does not occur here.

When the lesions on a leg in which phlebitis has occurred are examined, groups of small shiny papules, or sometimes vesicles, are often seen on the skin or surrounding an ulcer. These are always associated with pruritus, so that one begins calling them "itch papules." The tops of these papules are often bloody because of previous scratching by the patient. Fluorescein was injected intravenously into a number of patients with these lesions, and the skin was examined under filtered ultraviolet radiation.[5] The fluorescein appeared in much greater concentration in the scratched areas than in the intact skin. This was

Sequence of Events After the Occurrence of Thrombophlebitis


Venous Congestion
(Postphlebitic or incompetent veins)
Local increase in concentration of circulating allergens
Vascular allergy and venous thrombosis
Plus trauma with local outpouring of allergens
Clinical skin allergy
Ulcer on the leg

a visual demonstration of the concept of outpouring of allergens and other substances into traumatized areas (Auer [4]). This observation was of interest from the standpoint of a possible teleologic explanation as to why persons scratch a spot which itches. Scratching traumatizes the skin and possibly capillaries in it, so that quantities of the offending allergens escape into the traumatized skin. This may serve as a mechanism for removing the allergens from the general circulation into the skin, which is not a vital tissue. The observation with fluorescein illustrates the effect of even minor trauma on a phlebitic leg or one with varicose veins. Trauma will result in a local accumulation of allergens or bacteria in an extremity in which they are already in greater concentration than elsewhere.

One can easily demonstrate the increased sensitivity or sensitization of the leg in many patients who have had phlebitis. For example, many such patients will give a history of considerable sensitization to adhesive tape on the leg. If adhesive tape is applied, a severe reaction

5. Neller, J. L.: Use of Fluorescent Wheals in Determining Extent and Degree of Peripheral Vascular Insufficiency, Ann. Surg. **122**:898-901 (Nov.) 1945.

often occurs. In the normal leg there usually develops little or no reaction unless the patient is highly sensitive to the adhesive tape. One of the cases reported illustrates this (case 3, figs. 3 and 4). In several patients the injection of trichophytin intracutaneously, for example, resulted in a decided reaction in the leg which had been affected with phlebitis, with a much milder reaction in the normal leg (case 2, fig. 2). The application of drugs to an extremity after the occurrence of phlebitis is likely to result in sensitization because of failure of the drug

Fig. 1 (case 1).—Dermatitis due to sensitization of sulfathiazole in an extremity in which phlebitis had occurred.

to be removed rapidly as the result of the venous thrombosis or incompetence and also probably because of previous sensitization by other antigens.

REPORT OF CASES

Case 1.—H. M., a female patient, aged 38, was admitted to the Peripheral Vascular Clinic in November 1940, with a history of varicose veins for the past fifteen years and of an attack of thrombophlebitis in the left leg in 1935 following childbirth. The left leg continued swelling after the attack of phlebitis. No active treatment was carried out on her first visit to the clinic. She came

again in February 1941 with moist dermatitis of the lower part of both legs. She was then not seen again until September 1944, when she came to the clinic with an extensive dermatitis of the left leg (fig. 1). Severe pruritus had developed, and she had then applied sulfanilamide powder, which resulted in a severe eruption due to sensitization. On examination there were a number of oozing areas on the lower part of the left leg and urticaria on the right thigh. The patient appeared to be in extreme discomfort. Three paravertebral blocks were done in the left lumbar region over a period of three weeks, after which the tenderness over the veins disappeared and the dermatitis dried up. The patient stated that the leg felt better than it had felt for years. She came to the clinic again in January 1945, with the complaint that about a week prior to admission there had developed soreness and an eruption over an area of induration on the left leg, with severe pruritus. Two days later pruritus with papillary eruption appeared over the other extremities and the trunk. The chief complaint was

Fig. 2 (case 2).—Reaction to skin test with 0.1 cc. of extract of Trichophyton purpureum. There was a much greater reaction in the right leg in forty-eight hours, in which phlebitis had occurred.

pruritus, which appeared to be the result of sensitivity to an unknown allergen. There was nothing in the history to suggest the cause of the allergy. She was treated symptomatically with calamine lotion, corn starch baths, ephedrine sulfate and phenobarbital, with improvement.

This case illustrates the localization of allergic lesions in an extremity with postphlebitic involvement. With the onset of generalized pruritus and eruption, the first lesions appeared on the affected leg two days prior to involvement of the rest of the body, illustrating the tendency for greater concentration or accumulation of allergens in an area of venous congestion or the greater sensitivity of the extremity that had been affected by phlebitis.

Case 2.—C. T., a white woman, 39 years old, was first seen in the clinic in 1938, with a history of the occurrence of phlebitis in the right leg in 1934 follow-

ing a kick. The leg became swollen up to the hip and blue. In 1936 ulcers developed at the site of the injection into dilated veins. In 1938 an ulcer developed on the anterior part of the right leg, which was the reason for her coming into the clinic. She complained of severe pain and swelling. On examination the entire right leg was edematous and an ulcer 2 cm. in diameter was present on the anterior surface of the right leg, with hyperpigmentation for an area 15 cm. wide completely

Fig. 3 (case 3).—Reaction of skin on leg affected by phlebitis after adhesive tape was applied for three hours; illustration of dermatitis remaining in four blocked areas one week later.

around the leg. There were a number of incompetent veins which appeared to be communicating veins. Because of a great deal of dermatophytosis at various times, the patient was tested in October 1941 with an extract of Trichophyton purpureum in the right leg above the pigmented area and also in the left leg. The photograph (fig. 2) illustrates the difference in reaction to the same amount of

trichophytin (0.1 cc.). The reaction of the right leg was severe, covering an area approximately 10 cm. in diameter, and persisted for several weeks. The reaction in the left leg was much less extensive, covering an area approximately 5 cm. in diameter, and definitely less inflammatory.

CASE 3.—M. G., a white man, 40 years old, was admitted to the clinic in November 1945, with a history of phlebitis of the left leg following a fracture twenty years previously and an incision for resetting of the displaced bone in 1943. After the operation, the incision failed to heal and an ulcer remained on the left midleg anteriorly. On examination the left calf was 43.5 cm. in circumference and the right 41 cm. There was a hyperpigmented area over the lower half of the left leg, with a necrotic ulcer 8 cm. in diameter. There was a good deal of dermatophytosis between the toes. The treatment included paravertebral blocks, local administration of tyrothricin, applications of autogenous

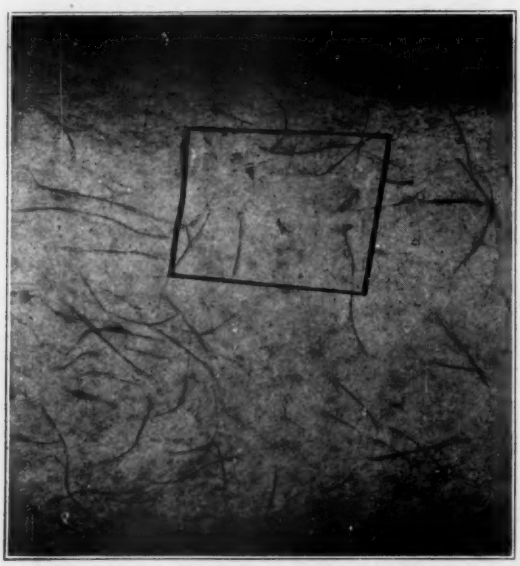


Fig. 4 (case 4).—After application of adhesive tape on patient's normal leg, there was no reaction.

blood, avoidance of tobacco and application of Castellani's paint. On one occasion the dressing applied to the ulcerated area was strapped down with adhesive tape, which was in contact with the skin in four places. When the patient returned to the clinic the following week, he stated that he had had to remove the adhesive tape as soon as he arrived home, three hours after its application, because of severe pruritus and discomfort. When he came in a week later the areas which were in contact with the adhesive tape were still inflamed (fig. 3). A piece of adhesive tape 2.5 cm. square was applied to the right or normal leg for three hours, during which time he had no symptoms; on removal there was no sign of any reaction (fig. 4).

This case illustrates the decided sensitivity to adhesive tape that is often present in extremities after phlebitis.

COMMENT

Our management of the extremity with postphlebitic involvement or of one with varicose veins with a lesion due to the stasis factor has been influenced by the concept expressed. For example, we now use cold solutions locally to cause vasoconstriction and reduce the quantity of allergens brought to the part. The patients feel better with cold applications. Rest, with elevation of the legs, has always been used in the treatment of extremities affected by phlebitis. These measures, by improving venous outflow, reduce the quantity of allergens and bacteria in the legs. The same reasoning applies to the benefit obtained from compression bandages, such as elastic stockings. Ligation of incompetent veins in the absence of major thrombosis of the deep veins often is of benefit by reducing back pressure.

Sulfonamide compounds or any other sensitizing type of drug should not be used on extremities with postphlebitic involvement, as they tend to concentrate there. Adhesive tape should never be applied directly to the skin of these extremities. Several patients have required hospitalization for several weeks as the result of having adhesive tape strapped on an ulcer, with development of a severe inflammatory reaction with edema and dermatitis on the greater part of the leg.

One of our active methods of treating the discomfort or fatigue often present in the legs of patients who have had phlebitis has been the injection of procaine hydrochloride into the lumbar sympathetic chain or ganglions. When patients began coming to the clinic with severe local reactions due to application of sulfathiazole, we were surprized to find that allergic conditions which might have been present for many months often cleared up after the injection of procaine hydrochloride into the lumbar sympathetic ganglions. This observation is being discussed in detail in a separate report.[6]

State and Wangensteen[7] have reported intravenous injections of procaine hydrochoride as being of benefit in acute serum reactions. The reactions had resulted from the attempt to use bovine albumin in human beings as a substitute for blood during the war. The injections also cleared up the urticaria present in 6 of 7 other patients. State and Wangensteen have given a number of theories as to how procaine hydrochloride may work to relieve these allergic conditions. One of their theories is that the drug causes vasodilatation due to action on the sympathetic nervous system. The relief obtained in our group of patients was the result of injection of procaine hydrochloride into

6. Naide, M.: Treatment of Certain Dermatologic Conditions by Paravertebral Ganglion Block, Arch. Dermat. & Syph., to be published.

7. State, D., and Wangensteen, O. H.: Delayed Serum Sickness, J. A. M. A. **130**:990-995 (April 13) 1946.

the sympathetic ganglions. However, we do not know how the drug acts to relieve allergic conditions. We do not believe that vasodilatation is the chief factor in improvement of these conditions, since the patients are often made worse by complete vasodilatation when they are in a tub of warm water. Their itching and dermatitis is usually aggravated. The method of action may be that which occurs when sympathetic ganglion block with procaine hydrochloride is carried out for causalgia and may be due to interruption of a cycle of irritating stimuli set up in the extremity and in the postphlebitic lesion. It is of interest to note a report by Coca [8] in 1944, who relieved severe gastrointestinal allergy in 6 patients by the Smithwick type of sympathectomy.

SUMMARY

The susceptibility of the extremity to allergic reactions after phlebitis is discussed. The clinical manifestations resulting from this susceptibility are described. Past thrombophlebitis or phlebothrombosis or incompetence of veins may result in trapping or accumulation of allergens as the result of venous congestion. The importance of a local circulatory factor in the localization of an allergic condition is emphasized.

Efforts to reduce arterial blood flow and also to increase venous outflow are important in treatment of allergic lesions in extremities with diseases of the veins. Removal of known allergens is important. Known sensitizing substances, such as the sulfonamide drugs, penicillin and adhesive tape, should not be used locally.

The use of paravertebral block of the regional sympathetic ganglions in treating lesions in extremities afflicted with phlebitis in the past or with varicose veins is described.

8. Coca, A. F.: Sympathectomy as an Aid in the Relief of Familial Nonreagenic Food Allergy, Ann. Allergy **2**:213-224 (May-June) 1944.

HEPATIC CIRRHOSIS AND TESTICULAR ATROPHY

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ALTHOUGH an increasing number of papers have appeared in recent years on the subject of atrophy of the testes and gynecomastia in cirrhosis of the liver, little of the work has been controlled by morphologic studies. Since atrophy and hyperplasia of tissues are to a large extent morphologic concepts, they cannot be completely evaluated without such studies. Glass, Edmondson and Soll,[1] for example, stated that of 14 males hospitalized for chronic disease of the liver there was gynecomastia in 8 and testicular atrophy in all, presumably on the basis of clinical examination. This can be deceptive, however, as the following instance will illustrate. In a recent case of active Laennec cirrhosis coming to autopsy here the combined weight of the testes was 21 Gm.; the usual weight for a man of the age of the patient is 30 to 40 Gm. It might have been supposed that well developed atrophy would be present. Yet microscopic studies showed that most of the tubules exhibited active spermatogenesis, with the production of mature sperm. In other tubules there were some early atrophic changes, which would be diagnosed as representing stage I under the terms of the scheme to be discussed later. This case is included in table 4 as an instance of active cirrhosis without atrophy. The problem should be given more attention from the morphologic standpoint. Since the changes are supposed to result from an excess of circulating estrogen, an ideal study should assess not only the weight and histologic appearance of the testes but also the condition of the prostate, seminal vesicles and breasts in men and the endometrium and breasts in women. Such an ideal study was not possible, but an attempt was made to analyze the material available.

A brief review and an abundance of references are to be found in a recent article by the Biskinds [2] which sums up the view that the liver normally inactivates estrogens and androgens and that in certain pathologic processes there is a selective loss of ability to inactivate estrogens. Interest in endocrine disturbances in cirrhosis of the liver was stimulated by the work of Glass, Edmondson and Soll,[1] whose bioassays of the urine

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1. Glass, S. J.; Edmondson, H. A., and Soll, S. N.: Sex Hormone Changes Associated with Liver Disease, Endocrinology **27**:749 (Nov.) 1940.

2. Biskind, G. R., and Biskind, M. S.: The Nutritional Aspects of Certain Endocrine Disorders, Am. J. Clin. Path. **16**:737 (Dec.) 1946.

of patients with advanced disease revealed elevated values for free estrogen, decreased values for combined estrogen and low or zero values for free androgen. Later the same investigators [3] reported that after the injection of estradiol and estrone into men with cirrhosis, a high percentage could be recovered in the urine, as compared with that recovered in normal male controls. As far as the changes in the tissues are concerned, the subject has been scantily treated in the journals on pathology. Morrione [4] has briefly reviewed what seem to be the only papers on this topic. He himself studied 28 cases of Laennec's cirrhosis and, in respect to the testes, graded the disease in 13 as "1 plus" atrophy, in 5 as "2 plus," in 9 as "3 plus" and in 1 as "no atrophy." He then chose control testes from persons of similar age groups by decades, the only other criterion of choice being absence of any disease known to predispose to testicular atrophy. After comparing the groups, he concluded that significant atrophy was present in 16 of his 28 cases and that in order to result in atrophy of the testes damage to the liver must be severe, extensive and of long standing.

The problem is approached in a somewhat different manner in the present paper. An attempt is made to correlate the testicular changes with the activity of the cirrhotic process as judged by histologic criteria. The criteria used here for diagnosing "active" cirrhosis are those set forth by Moon.[5] The presence of Mallory bodies is the most important and constant single feature. Also indicative of activity are disintegrating parenchymal cells, active proliferation of bile ducts, infiltration by polymorphonuclear cells in areas of cell destruction and fibrous tissue, formation of new fibrous tissue and signs of parenchymal cell regeneration. Fat is not considered indicative of activity. It is usually absent in the rapidly progressing cirrhosis of childhood and varies greatly in amount in adult cirrhosis without always correlating with other signs of activity.

MORPHOLOGIC ALTERATIONS IN TESTICULAR ATROPHY

This subject is exhaustively treated by Obendorfer in the handbook of Henke and Lubarsch.[6] Except in testicular atrophy due to roentgen irradiation, in which a selective first effect is exerted on spermatogonia and spermatocytes, with sparing of spermatids and sperm, the cells disappear in regular order of maturity, associated with certain other changes.

3. Glass, S. J.; Edmondson, H. A., and Soll, S. N.: Excretion of Estrogen After Injection of Estradiol and Estrone into Men with Cirrhosis of the Liver, J. Clin. Endocrinol. **4**:54 (Feb.) 1944.

4. Morrione, T. G.: Effect of Estrogens on the Testis in Hepatic Insufficiency, Arch. Path. **37**:39 (Jan.) 1944.

5. Moon, V. H.: Atrophic Cirrhosis, Arch. Path. **13**:691 (May) 1932.

6. Obendorfer, S., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1931, vol. 6, pt. 3, pp. 605-626.

On this basis the stage of the atrophy may be designated by a number. In stage I sperm are largely absent, spermatids may be slightly increased in number and abnormal spermatids may be present. In stage II spermatids are decreased in number and form syncytial masses and giant cells *(Spermidenriesenzellen),* and varying degrees of phagocytosis occur. In stage III the spermatocytes decrease and disappear, in stage IV the spermatogonia disappear and in stage V the Sertoli cells disappear. Obendorfer stated that occasionally sperm may persist in the tubules for a long time and even be found attached to Sertoli cells. This is rather unusual, however. In association with these changes in the character of the germinal epithelium there is a progressive diminution in the diameter of the tubules, with thickening and hyalinization of the membrana propria. To some extent the closely related stages may coexist in different tubules and even in different parts of the same tubule. The atrophic changes are often further developed near the rete testis. Nevertheless, the process with which I am here concerned is a generalized one, and I have not diagnosed as atrophic those testes which had a few small areas of completely fibrotic tubules when the remainder showed complete spermatogenesis. In addition to the changes so far described there may be an apparent or real increase in the number of Leydig cells and in their pigment content, together with a decrease in the number of interstitial connective tissue cells and varying degrees of interstitial fibrosis and hyalinization. Obendorfer briefly discusses (1) the focal atrophy and fibrosis of senility and vascular sclerosis, characteristically showing tubules with active spermatogenesis lying beside others which are completely fibrosed; (2) atrophy associated with inflammatory diseases of the testis and epididymis; (3) generalized, usually mild atrophy resulting from an increase of temperature, as in fever; (4) atrophy associated with pulmonary tuberculosis and other wasting diseases, inconstant and often focal; (5) atrophy of the tubules with great edema of the interstitial connective tissue, seen in famine edema; (6) mild generalized atrophy or suppression of spermatogenesis as a result of sexual abstinence, the data in relation to this being derived from the study of the testes of young soldiers dying in battle after several months of unrelieved front line trench warfare as compared with the testes of young civilians after sudden death; (7) atrophy associated with chronic alcoholism, which is inconstant, often focal and not definitely attributable to alcohol; (8) atrophy associated with schizophrenia and (9) atrophy associated with cirrhosis of the liver. As regards this last category, Obendorfer mentioned only the papers of Kyrle[7] and Weichselbaum,[8] as have other writers on the subject.

7. Kyrle, J.: Ueber Structuranomalien im menschlichen Hodenparenchym; Verhandl. d. deutsch. path. Gesellsch. **13**:391, 1909.

8. Weichselbaum, A.: Ueber Veränderungen der Hoden bei chronischem Alkoholismus, Verhandl. d. deutsch. path. Gesellsch. **14**:234, 1910.

There seems to be little else to mention. These investigators were the first to observe the phenomenon; however, they attributed the changes to chronic alcoholism, rather than to cirrhosis.

TABLE 1.—*Active Laennec Cirrhosis with Testicular Atrophy*

	Liver						Testis			
Age of Patient, Yr.	Weight, Gm.	Fibrosis	Mallory Bodies	Biliary Hyperplasia	Cellular Infiltration	Fat	Germinal Epithelium	Leydig Interstitial Cells	Interstitial Fibrosis	Stage of Atrophy
58	2,020	2+	1+	3+	PMN 2+ L 4+	2+	No SP No SPT Few SPC	Pigment 1+	1+	III
47	2,410	2+	1+	3+	PMN 2+ L 4+	3+	No SP No SPT Few SPC	NR	NR	III
63	1,720	3+	1+	2+	PMN 0 L 2+	2+	No SP No SPT Few SPC	Pigment 1+	NR	III
51	1,460	3+	Autolysis ?	2+	PMN 0 L 2+	2+	Autolysis No SP No SPT	NR	1+	II
45	1,720	2+	2+	2+	PMN 2+ L 4+	2+	No SP No SPT Many SPC	Pigment 1+	NR	II
41	2,460	2+	1+	2+	PMN 2+ L 4+	2+	No SP No SPT Many SPC	NR	NR	II
35	2,460	3+	1+	3+	PMN 1+ L 3+	3+	No SP No SPT Many SPC	Hyperplasia	NR	II
62	3,430	2+	1+	2+	PMN 1+ L 3+	3+	No SP No SPT Many SPC	NR	3+	II
67	2,210	2+	2+	2+	PMN 1+ L 3+	3+	No SP No SPT Few SPC	NR	NR	III
54	2,050	1+	2+	2+	PMN 2+ L 4+	2+	No SP No SPT Few SPC	NR	NR	III
52	1,565	1+	3+	2+	PMN 2+ L 4+	1+	No SP No SPT Few SPC	NR	NR	III
43	4,100	1+	2+	2+	PMN 0 L 1+	3+	No SP No SPT Many SPC	Hyperplasia	NR	II
53	2,400	2+	Autolysis ?	2+	PMN 1+ L 2+	2+	No SP No SPT Many SPC	NR	3+	II
52	2,040	1+	3+	2+	PMN 1+ L 2+	2+	No SP No SPT Few SPC	NR	NR	III
39	1,120	2+	2+	2+	PMN 1+ L 3+	2+	No SP No SPT Few SPC	Pigment 1+	1+	III
56	1,730	2+	4+	2+	PMN 1+ L 3+	2+	No SP No SPT Few SPC	NR	1+	III
43	2,225	1+	2+	2+	PMN 1+ L 3+	1+	No SP Rare SPT Many SPC	NR	1+	II

Abbreviations: SP, sperm; SPT, spermatid; SPC, spermatocyte; NR, not remarkable; PMN, polymorphonuclear leukocytes; L, lymphocytes.

RESULTS

A high incidence of testicular atrophy was found in cirrhosis judged active by histologic criteria (tables 1 and 4). It occurred in 17 of 20 cases. Similar atrophy was found in only 5 of the 15 cases of

TABLE 2.—*Inactive Laennec Cirrhosis with Testicular Atrophy*

	Liver						Testis			
Age of Patient, Yr.	Weight, Gm.	Fibrosis	Mallory Bodies	Biliary Hyperplasia	Cellular Infiltration	Fat	Germinal Epithelium	Leydig Interstitial Cells	Interstitial Fibrosis	Stage of Atrophy
57	1,015	3+	0	1+	PMN 1+ L 2+	1+	No SP No SPT Many SPC	NR	0	II
57	1,260	3+	0	2+	PMN 0 L 1+	0	No SP No SPT Few SPC	NR	0	III
76	880	4+	0	2+	PMN 0 L 2+	0	No SP No SPT Few SPC	NR	0	III
37	735	3+	0	1+	PMN 0 L 1+	0	No SP No SPT Few SPC	NR	1+	III
67	1,000	3+	0	2+	PMN 0 L 3+	0	No SP No SPT Few SPC	NR	0	III

Abbreviations: See table 1.

TABLE 3.—*Inactive Laennec Cirrhosis Without Testicular Atrophy*

	Liver						Testis			
Age of Patient, Yr.	Weight, Gm.	Fibrosis	Mallory Bodies	Biliary Hyperplasia	Cellular Infiltration	Fat	Germinal Epithelium	Leydig Interstitial Cells	Interstitial Fibrosis	Stage of Atrophy
42	1,950	3+	0	3+	PMN 0 L 3+	0	SP SPT SPC	NR	NR	No atrophy
29	2,370	1+	0	1+	PMN 0 L 2+	0	SP SPT SPC	NR	NR	No atrophy
66	1,700	2+	0	1+	PMN 0 L 2+	1+	SP SPT SPC	NR	NR	No atrophy
45	2,420	2+	0	1+	PMN 0 L 2+	2+	SP SPT SPC	NR	NR	No atrophy
59	1,620	1+	0	1+	PMN 0 L 1+	2+	SP SPT SPC	NR	NR	No atrophy
48	2,320	2+	0	1+	PMN 0 L 1+	0	SP SPT SPC	NR	NR	No atrophy
83	2,000	2+	0	1+	PMN 0 L 1+	0	SP SPT SPC	NR	NR	No atrophy
78	1,400	1+	0	1+	PMN 0 L 1+	0	SP SPT SPC	NR	NR	No atrophy
57	1,220	2+	0	2+	PMN 0 L 2+	0	SP SPT SPC	NR	NR	No atrophy
48	1,950	1+	0	1+	PMN 0 L 1+	1+	SP SPT SPC	NR	NR	No atrophy

Abbreviations: See table 1.

inactive cirrhosis (tables 2 and 3). The ages in the group with active disease ranged from 35 to 67 years, averaging 51.7 years. In the group with inactive cirrhosis the range was from 29 to 83, with an average of 56.7 years. In neither series was there significant local disease of the testis or epididymis or any other condition known to predispose to testicular atrophy.

COMMENT AND CONCLUSIONS

It appears that the testicular atrophy associated with Laennec's cirrhosis occurs in the phase of histologic activity of the hepatic lesion. This atrophy associated with the active phase is not invariable (table 4), is not complete (no atrophy in stage IV or V was seen) and apparently is reversible when histologic inactivity supervenes. It may be said also that the appearance of the germinal epithelium does not always correlate with the weight of the testes. This statement is made on the basis of

TABLE 4.—*Active Laennec Cirrhosis Without Testicular Atrophy*

		Liver					Testis			
Age of Patient, Yr.	Weight, Gm.	Fibrosis	Mallory Bodies	Biliary Hyperplasia	Cellular Infiltration	Fat	Germinal Epithelium	Leydig Interstitial Cells	Interstitial Fibrosis	Stage of Atrophy
60	2,100	2+	2+	2+	PMN 1+ L 2+	2+	SP SPT SPC	NR	NR	No atrophy
53	900	1+	1+	1+	PMN 1+ L 2+	1+	SP SPT SPC	NR	NR	No atrophy
61	1,800	2+	3+	1+	PMN 1+ L 2+	4+	SP SPT SPC	NR	NR	No atrophy

Abbreviations: See table 1.

only 1 case, previously mentioned. In this instance (table 4, second case) there was a history of exacerbations and remissions, death finally occurring as a result of hemorrhage from an esophageal varix during a phase of renewed histologic activity of the hepatic lesion.

It is not the purpose of this paper to discuss the validity of the hypothetic endocrine disturbance generally cited as the cause of the testicular atrophy in Laennec's cirrhosis, but simply to determine to what extent and in what circumstances it occurs. However, it should be mentioned that there were no instances of gynecomastia in this series. Admittedly the search for gynecomastia has been most carefully conducted only in recent years and might have been overlooked at one time. Hyperplasia of Leydig cells was found in 2 cases (table 1). Because of the variation in the number of Leydig cells in a variety of conditions,[9] it is difficult to weigh such a finding.

9. Warren, S., and Olshausen, K. W.: Interstitial Cell Growths of the Testicle, Am. J. Path. **19**:307 (March) 1943.

INCIDENCE OF TUBERCULOUS PULMONARY CAVITIES IN UNEXPECTED DEATHS INVESTIGATED AT NECROPSY

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THE EPIDEMIOLOGY of tuberculosis may be investigated in four ways. The most frequent method is to determine mortality rates from information contained in death registrations. In this manner large numbers of cases may be obtained, but there are two sources of error in such data to which little attention has been given. Practically all causes of death are based on clinical and not on pathologic diagnosis, and pathologists are aware of the inaccuracies which are apt to be present in such data. Even if the clinical diagnosis of the cause of death is correct, this does not exclude the possibility that active pulmonary tuberculosis was present and that tubercle bacilli were being excreted—an important condition when the epidemiology of the disease is considered. A second procedure is the tuberculin survey, from which the rate of infection may be accurately determined and from which suggestions arise as to where to search for "contact" cases. Unfortunately, most tuberculin surveys have been limited to the period of youth, and the data obtained can be used only in connection with that period. Mass roentgen surveys of the chest is a third method which, although intended primarily for the purpose of detecting clinically active tuberculous disease, may be of value in epidemiologic studies, provided all persons in a community are included and correct interpretations of pulmonary shadows are made. Two facts should always be borne in mind in reading roentgenograms of the chest. The early tuberculous focus, speaking in terms of the pathologic process, is too small and too delicate in texture to cause a shadow on the film, and it is not often that a correct diagnosis of structurally healed tuberculosis in the so-called reinfection type of disease can be made from roentgenographic shadows. Necropsy records are a fourth source of information and are of considerable epidemiologic value. These records are seldom consulted in epidemiologic studies, probably because of their

This work was sponsored by the Hegeman Research Fund.

The data discussed in this paper were made available through the courtesy of the Medical Examiner's Office of the Borough of Manhattan.

limited number, but in them are to be found the most accurate data available relative to anatomically significant tuberculous disease. It is not sufficiently appreciated that many pathologic changes, including formation of cavities, often are recorded in the anatomic diagnosis without tuberculosis appearing as the main or even as a contributing cause of death in death registries. Data from anatomic sources of information only will be analyzed in this study.

METHOD AND MATERIAL

In the past two and one-half years I have had the privilege of examining tissues for signs of tuberculous infection in cases investigated post mortem by the Medical Examiner's Staff of the Borough of Manhattan. The investigation covered unexpected, usually sudden deaths,

TABLE 1.—*Incidence of Tuberculous Pulmonary Cavities According to Age and Race in 1,332 Persons Examined, 1944-1946*

				Race					
	Total			White			Negro		
Age	Total	Number with Tuberculous Cavity	Percentage with Tuberculous Cavity	Total	Number with Tuberculous Cavity	Percentage with Tuberculous Cavity	Total	Number with Tuberculous Cavity	Percentage with Tuberculous Cavity
Total.....	1,332	61	4.58	1,038	51	4.9	294	10	3.4
3 mos. to 9 yrs.	43	..	.....	30	..	...	13	..	...
10 to 19 yrs.....	64	..	.....	27	..	...	37	..	...
20 to 29 yrs.....	148	2	1.35	85	1	1.2	63	1	1.6
30 to 39 yrs.....	200	11	5.5	132	5	3.8	68	6	8.8
40 to 49 yrs.....	293	16	5.46	234	14	5.9	59	2	3.4
50 to 59 yrs.....	275	17	6.18	239	16	6.7	36	1	2.8
Over 60 yrs.....	309	15	4.85	291	15	5.2	18	..	...

only a few of which involved hospitalized patients. Persons with extensive pulmonary disease other than tuberculosis and bodies which showed advanced postmortem decomposition were excluded. With these exceptions, representing less than 5 per cent of the material available, each person was thoroughly studied for evidence of tuberculous infection, from one and one-half to two hours being required to complete an examination. A record of the lesions and preservation of diseased tissue for future study were made in each case. The main purpose of the study was to determine the incidence of tuberculous infection and the status of the lesions. In this report only cases in which tuberculous cavities were present in the lungs will be discussed, because from an epidemiologic standpoint these were the persons who were excreting tubercle bacilli at the time of their deaths.

A total of 1,332 persons were examined, of whom 1,038 were white and 294 were Negroes. Persons over 3 months of age were included. In this group there were 61 (4.58 per cent) with tuberculous cavities in the lungs. Table 1 shows the distribution according to age and race.

Cavity formation was found somewhat more often in the white persons than in the Negroes, the ratio being 1.4 to 1. No cavity formation was found in persons under 20 years of age. Three fourths of the subjects with cavities were white persons over 40 years of age.

TABLE 2.—*Incidence of Pulmonary Tuberculous Cavities in 294 Negroes Examined*

	Total			Sex					
				Male			Female		
Age	Total	Number with Tuberculous Cavity	Percentage with Tuberculous Cavity	Total	Number with Tuberculous Cavity	Percentage with Tuberculous Cavity	Total	Number with Tuberculous Cavity	Percentage with Tuberculous Cavity
Total.....	294	10	3.4	193	7	3.6	101	3	2.97
3 mos. to 9 yrs.	13	..	...	7	..	...	6	..	...
10 to 19 yrs.....	37	..	...	27	..	...	10	..	...
20 to 29 yrs.....	63	1	1.6	36	..	...	27	1	3.7
30 to 39 yrs.....	68	6	8.8	40	5	12.5	28	1	3.6
40 to 49 yrs.....	59	2	3.4	40	1	2.5	19	1	5.3
50 to 59 yrs.....	36	1	2.8	29	1	3.4	7	..	...
Over 60 yrs.....	18	..	...	14	..	...	4	..	...

TABLE 3.—*Incidence of Pulmonary Tuberculous Cavities in 1,038 White Persons Examined*

	Total			Sex					
				Male			Female		
Age	Total	Number with Tuberculous Cavity	Percentage with Tuberculous Cavity	Total	Number with Tuberculous Cavity	Percentage with Tuberculous Cavity	Total	Number with Tuberculous Cavity	Percentage with Tuberculous Cavity
Total.....	1,038	51	4.9	790	49	6.2	248	2	0.8
3 mos. to 9 yrs.	30	..	...	20	..	...	10	..	...
10 to 19 yrs.....	27	..	...	22	..	...	5	..	...
20 to 29 yrs.....	85	1	1.2	47	..	...	38	1	2.6
30 to 39 yrs.....	132	5	3.8	78	4	5.1	54	1	1.85
40 to 49 yrs.....	234	14	5.98	183	14	7.6	51	..	...
50 to 59 yrs.....	239	16	6.7	207	16	7.7	32	..	...
Over 60 yrs.....	291	15	5.2	233	15	6.4	58	..	...

Tables 2 and 3 show the distribution of subjects according to age and sex in the different races. There was little difference in relation to sex among the Negroes. Among white persons, males exhibited cavity formation 7.7 times more often than females, or almost twice as often as Negroes. Nine of every 10 white males with cavity formation were over 40 years of age.

The causes of death as filed in the office of the Medical Examiner for the Borough of Manhattan are shown in table 4 for 61 persons.

Although each of the 61 had tuberculous cavity formation and endobronchial spread, in only 13 instances was death registered as due to tuberculosis. It is the duty of the pathologists who perform the necropsies to determine the immediate cause of death, and the cause of death as filed may be regarded as accurate. This table shows data relative to important facts in the epidemiology of tuberculosis which may be absent from death registries. It also indicates the wide range of patho-

TABLE 4.—*Causes of Death in Persons with Tuberculous Pulmonary Cavities as Recorded in the Medical Examiner's Office*

Natural causes		27
Tuberculosis	13	
Neoplasm	3	
Coronary occlusion	3	
Lobular pneumonia	2	
Brain abscess	1	
Acute encephalitis	1	
Acute endocarditis	1	
Sickle cell anemia	1	
Exhaustive psychosis	1	
Generalized atherosclerosis	1	
Traumatic deaths		21
Alcoholism, acute and chronic		7
Homocide		2
Suicide		1
Drowning		1
Carbon monoxide poisoning		1
Barbiturate poisoning		1

TABLE 5.—*Location of Tuberculous Pulmonary Cavities (Seventy-Seven Cavities in Sixty-One Persons)*

Upper lobes		67
Right lung (apical, 11; subapical, 25)	36	
Left lung (apical, 10; subapical, 21)	31	
Lower lobes (all in upper third of lobe)		9
Right lung	5	
Left lung	4	
Middle lobe of the right lung (upper part of lobe)		1

logic processes which are encountered in cases that come under the supervision of the Medical Examiner's Office. In the absence of evidence obtained by necropsy or biopsy, vital statistics are of limited value.

In the majority of the cases under discussion the tuberculous process in the lungs was rather limited in extent, the remainder of the pulmonary tissue being free from any major disease. This condition afforded an opportunity to study the location of the cavities in relation to their position within the lungs and within the respective lobes. In table 5 the location of the cavities is shown. In 87 per cent of the cases the cavities were in the upper lobe, two thirds of them being

infraclavicular and one third apical in position. This coincides with the pattern of pulmonary tuberculosis commonly observed in roentgenograms of the chests of adults with clinical signs of disease. In other words, this group of 61 persons presents the typical picture of so-called reinfection tuberculosis.

Since the pulmonary tissue not involved in the tuberculous process was normal in the majority of instances, an opportunity was afforded to search for calcified parenchymal foci and for evidence of healed primary complexes. In every person examined all thoracic and abdominal lymph nodes were investigated for evidence of caseation, calcification and fibrosis. In general, it is accepted that the presence of only caseous foci in lymph nodes is evidence of a primary infection and that the presence of only calcified foci is evidence of a healed primary infection.

TABLE 6.—*Condition of Thoracic Lymph Nodes in Persons with Tuberculous Pulmonary Cavity According to Age and Race*

Age, Yr.	Total			Condition Found in Lymph Nodes								
				Caseous Foci			Calcified Foci			No Caseous or Calcified Foci		
	Total	White	Negro	Total	White	Negro	Total	White	Negro	Total	White	Negro
Total	61	51	10	16	9	7	27	25	2	18	17	1
20 to 29	2	1	1	2	1	1	..	..	..	..	..	..
30 to 39	11	5	6	5	2	3	4	2	2	2	1	1
40 to 49	10	14	2	6	4	2	4	4	..	6	6	..
50 to 59	17	16	1	2	1	1	9	9	..	6	6	..
Over 60	15	15	..	1	1	..	10	10	..	4	4	..

The condition of the lymph nodes in persons with cavity formation is presented in table 6 according to age and race. According to accepted methods of differentiating between primary and reinfection tuberculosis, 16 persons presented progressive primary tuberculosis, the youngest subject being 22 years of age and the oldest 68. Twenty-seven persons had structurally healed primary infections and had acquired a progressive new disease, the youngest subject being 33 years of age and the oldest 76. In 18 cases it was not possible to state whether a primary disease or reinfection was represented, because no evidence of caseation or calcification was observed in any node. In this group the youngest subject was 34 years of age and the oldest 81.

The difference between the races in changes in lymph nodes is apparent. Seven of the 10 Negroes had caseous nodes, whereas caseous nodes were present in only 17.6 per cent of the white persons. Calcified foci and absence of macroscopic disease in lymph nodes were found oftener in white persons.

COMMENT

There are many circumstances in which it is mandatory for the Medical Examiner's Office to assume jurisdiction over dead bodies. Deaths from various accidents, deaths occurring on arrival or within twenty-four hours after arrival of the patient at a hospital, homicidal and suicidal deaths and deaths occurring without the attendance of a physician all come within the scope of the Medical Examiner's jurisdiction. All the cases are handled through one office; complete postmortem examinations are performed in all instances in which crime is suspected, in all accidentals deaths in which litigation seems to be probable and in all instances in which the cause of death is obscure or unknown. Approximately 6,000 cases are handled yearly, and in about 20 per cent complete postmortem examinations are performed. It was from this material that the data presented here were obtained. The persons involved came from all parts of the Borough of Manhattan, although their legal residences may or may not have been within the Borough. Many occupations are represented. Among the persons with tuberculous cavity formation there were a garage mechanic, an elevator operator, a waiter, an accountant, a street peddler, a sailor, a truck driver and a saleslady, to mention a few. There is no "loading" of cases from the Negro district or from the indigent class. If the majority of the persons were in the lower income bracket, this condition per se was not the reason why they came under the jurisdiction of the Medical Examiner's Office, nor was it any indication that they had always been in the low income group. It is the opinion of the Medical Examiner's Office that these persons represent a fair, though small, cross section of the inhabitants of the Island of Manhattan.

It was unusual to find that the tuberculous cavity formation had been correctly diagnosed and properly treated. Of the 61 cases, in only 6 had the disease been clinically diagnosed as tuberculosis, and tuberculosis was listed as the cause of death in but 2 of the 6. In a few instances the disease was so extensive that the patients would eventually have died from it, yet tuberculosis nevertheless was not the cause of death. It would seem from these data that while mortality rates from tuberculosis are valuable they represent but one phase of the problem, which from an epidemiologic standpoint may not be as important as the detection of unrecognized spreaders of tubercle bacilli as revealed at necropsy.

The reasons for the preponderance of white men over 40 years of age with tuberculous cavities are not apparent, but there is an indication of what group of the adult population contains the greatest number of unknown spreaders of infection. If one may judge from the place of residence and type of employment, the spread of the

bacilli is general rather than local. This presents one of the most difficult problems in the epidemiologic control of tuberculosis.

The attempt to separate the disease into two types, i.e., progressive primary infection and progressive disease acquired after a primary infection had healed, was only partially successful, 16 persons apparently having primary infections and 27 reinfections in adult life. In the remaining 18 persons the disease was left unclassified, although some of them did show small calcified parenchymal foci which might be regarded as healed primary lesions. I do not regard such foci as necessarily representing healed primary infections, because it is known that small lesions in endobronchial spreads of the disease may calcify. This condition was shown definitely in 1 instance in this series, in which a person had been treated on several occasions for pulmonary tuberculosis over a period of twenty years, with roentgenograms of the chest available for seventeen years. After he was killed in an automobile accident, postmortem examination showed small calcified foci in three separate areas, representing the original site of disease and in two areas in which new disease was noted in roentgenograms thirteen and seventeen years after the disease was first diagnosed. In such circumstances no reliance can be placed on calcified parenchymal lesions without calcified foci in lymph nodes in the natural path of drainage as indicative of a first or of a subsequent infection. From these postmortem studies, it is evident that it is difficult and at times impossible to determine in an adult whether progressive tuberculosis represents a first or a subsequent infection. To make this differentiation by the appearance of shadows in a roentgenogram seems not to be warranted. It appears that progressive tuberculosis may develop at any age in an adult and that the clinical differentiation between "primary" and "reinfection" disease is of academic interest rather than of practical importance. A fact that is of significance in the epidemiology of the disease is that adults even in the sixth and seventh decades may contract tuberculosis and die from it.

Frequently a history of contact with a known tuberculous patient cannot be elicited from an adult with clinical tuberculosis, especially in urban areas. When a positive reaction to tuberculin occurs in a child, the home and its environs become the center of investigation in the search for "contact" cases. When clinical tuberculosis is discovered in an adult, the community as a whole should become the center of investigation for unrecognized "spreaders" of the infection. In such an investigation taverns, the eating houses, crowded places of amusement and public conveyances are of equal importance with the place of work. The data presented from this relatively small group of cases from the Medical Examiner's Office of the Borough of Manhattan indi-

cate the complexity of the problem of tuberculosis in the adult population. The solution of this problem requires the development of a comprehensive and realistic program of action.

SUMMARY

A study of records of 1,332 postmortem examinations from the Medical Examiner's Office of the Borough of Manhattan revealed 61 persons (4.58 per cent) with tuberculous cavities in the lungs. No tuberculous cavity was found in persons under 20 years of age. Forty-nine of the 61 persons with cavities were white males, 45 of whom were over 40 years of age. All of them presented the pattern of phthisis, i.e., so-called reinfection or adult tuberculosis with endobronchial spread. So far as it is possible to determine from postmortem examinations, the group was composed of persons with progressive primary infection, persons with progressive new infections acquired after a former infection had healed and persons with progressive disease of an indeterminate nature.

News and Comment

GENERAL NEWS

Mississippi Valley Medical Society.—The Twelfth Annual Meeting of the Mississippi Valley Medical Society will be held at the Municipal Auditorium, Burlington, Iowa, October 1, 2 and 3. Clinical teachers from leading medical schools will conduct the postgraduate assembly. The program is planned to appeal to general practitioners. There will be technical and scientific exhibits, a round table luncheon and a banquet preceded by a social hour. Dr. Edward L. Bortz, President of the American Medical Association, will be the principal banquet speaker together with the presidents of the Illinois, Iowa and Missouri state medical societies. For the first time in the history of the organization, a registration fee will not be charged. All ethical physicians are cordially invited to attend. A detailed program may be obtained from the secretary, Dr. Harold Swanberg, 209-224 W. C. U. Bldg., Quincy, Ill.

Mississippi Valley Medical Society Essay Contest.—Steven O. Schwartz, M.S., M.D., and Berthe E. Armstrong, M.D., of the Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, are the winners of the 1947 Mississippi Valley Medical Society Essay Contest "for the best unpublished essay on a subject of practical and applicable value to the general practitioner of medicine." Drs. Schwartz and Armstrong wrote on "Treatment of Iron Deficiency (Hypochromic Anemia)." They will receive a cash award, a gold medal and a certificate of award and will present their essay at the annual meeting in October. Their paper will appear in the January 1948 issue of the Society's official publication, the *Mississippi Valley Medical Journal.*

Mississippi Valley Medical Editors' Association.—The Fourth Annual Meeting of the Mississippi Valley Medical Editors' Association will be held at Hotel Burlington, Burlington, Iowa, Wednesday evening, October 1. A number of well known medical editors will speak. A discussion period will follow each paper. All interested in medical writing are cordially invited to attend. There will be no registration fee. A detailed program may be secured from the secretary, Harold Swanberg, M.D., 209-224 W. C. U. Bldg., Quincy, Ill.

Research Fellowships, The American College of Physicians.—The American College of Physicians announces that a limited number of fellowships in medicine will be available from July 1, 1948 to June 30, 1949. These fellowships are designed to provide an opportunity for training in research either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in internal medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work.

The stipend will be from $2,200 to $3,000. Application forms will be supplied on request to the American College of Physicians, 4200 Pine Street, Philadelphia 4,

Pa., and must be submitted in duplicate not later than Nov. 1, 1947. Announcement of the awards will be made as promptly as possible.

The American College of Physicians Announces Its Annual Session at San Francisco, April 19 to 23, 1948.—The American College of Physicians will conduct its twenty-ninth Annual Session at San Francisco, April 19 to 23, 1948. General headquarters will be at the Civic Auditorium. Dr. William J. Kerr and Dr. Ernest H. Falconer, both of San Francisco, are the co-chairmen for local arrangements and the program of clinics and panel discussions. The President of the College, Dr. Hugh J. Morgan, Professor of Medicine at Vanderbilt University School of Medicine, Nashville, Tenn., is in charge of the program of morning lectures and afternoon general sessions.

Secretaries of medical societies are especially asked to note these dates and, in arranging meeting dates of their societies, to avoid conflicts with the meeting of the American College of Physicians, for obvious mutual benefits.

Correspondence

ERUPTIVE FEVER

To the Editor:—In the ARCHIVES (May 1947) there appeared on pages 475 and 510 two interesting articles by S. H. Soll and Wright, Gold and Jennings respectively about eruptive fever (Stevens-Johnson syndrome).

I should like to point out that in 1937 I described 2 similar cases in *Ugeskrift for læger,* page 973, which might be of interest. Unfortunately they were not published in English, so they do not appear in the résumé of cases compiled from the literature.

My cases involved two young people, a male and a female. They had generalized erythema multiforme (?) and slight pneumonia, but the most characteristic features were diffuse purulent stomatitis, severe conjunctivitis, with injection of the sclera bulbi, which were a diffuse fiery red, and purulent vulvitis and balanitis respectively.

These cases must come under group II of Soll's article, as there were severe complications.

However, there was one complication which was not mentioned in the articles in the ARCHIVES. Tuberculosis of the lungs developed in both patients in a few months after they were discharged from the hospital. I must admit that it was an accidental finding. One of the patients was admitted to the hospital for another reason, and it was then that I discovered that she had tuberculosis. I then remembered the other patient and asked him to come to see me, and I made the same discovery.

I feel that this must be a rare condition indeed, as I have never since come across any other cases of this sort, although about 40,000 patients have passed through my hands.

I have therefore been unable to ascertain if the tuberculosis which my two patients had was a coincidence or if there is any real connection between tuberculosis and this special syndrome.

W. THUNE ANDERSEN, M.D., Svendborg, Denmark.

Q FEVER

To the Editor:—Some time ago the ARCHIVES OF INTERNAL MEDICINE (**76**:328, 1945) published an article of mine purporting to describe an outbreak of primary atypical pneumonia observed in Italy early in 1944.

More recently, I encountered in the *American Journal of Hygiene* (**44**:6, July, 1946) a series of interesting studies on Q fever as it appeared among troops in and returning from Italy. A comparison of the clinical features of the cases described by Robbins and Ragan (*Am. J. Hyg.* **44**:6 [July] 1946) and Feinstein and others (ibid. **44**:72 [July] 1946) with those I published in the ARCHIES leads me to the belief that my patients suffered from Q fever. Clinically, the rather sudden onset, early headache, duration and type of fever, paucity of physical findings in the chest, roentgenologic picture and lack of formation of cold agglutinins were characteristic of all the descriptions.

Though the matter is now largely of historic interest, for the sake of accuracy I felt that it may wisely be called to your attention and that perhaps a note should be made of it.

JACOB GROSSMAN, M.D., New York.

Montefiore Hospital for Chronic Diseases.

Obituaries

JOHN H. MUSSER, M.D.

1883-1947

With deep regret, the ARCHIVES announces the death of Dr. John Herr Musser at New Orleans on Sept. 5, 1947, a member of its editorial board for the past fifteen years.

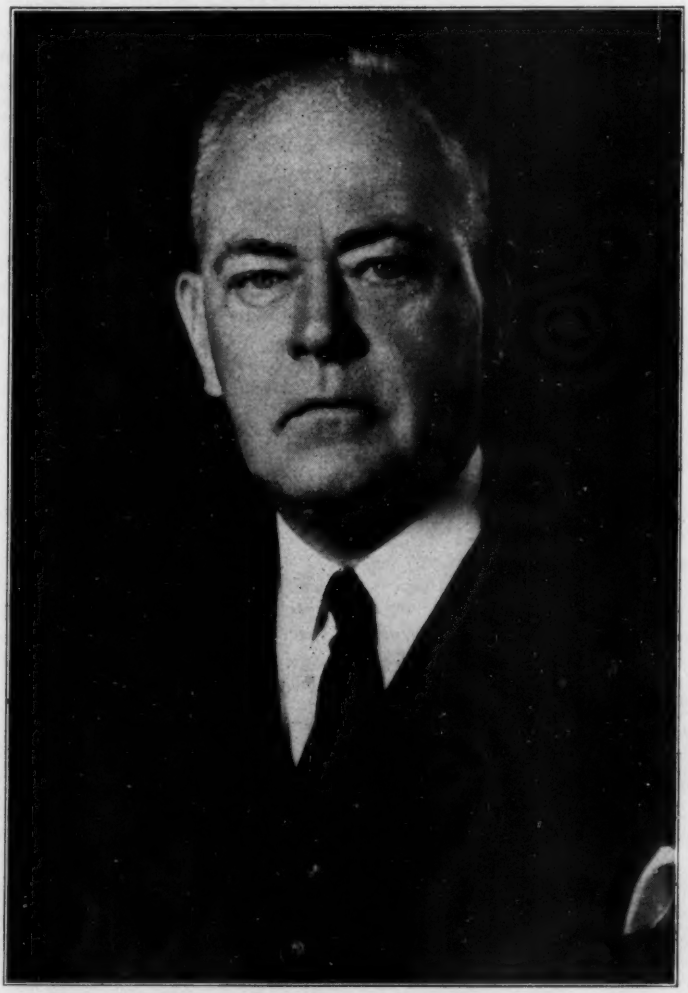
Dr. Musser was the sixth John Musser in direct line to enter the profession of medicine; he seemed born and bred for a successful medical career. He was brought up in Philadelphia, graduating from the University of Pennsylvania in 1905 as a Bachelor of Science and in 1908 as a Doctor of Medicine. His promise as a teacher of clinical medicine soon was recognized so that he began his academic career early in life, finally serving from 1919 to 1924 as assistant professor of medicine at his medical school.

In 1924 he was invited to become professor of medicine at the Tulane University of Louisiana in New Orleans and here, in this chair, were spent the most productive years of his life. His clinical judgment was sound, so that his opinion was widely sought in consultation. His students appreciated the manner in which he taught: always as a clinician, not allowing theory to outweigh experience and never forgetting the personal relations that exist between physician and patient. He developed an unforeseen talent for administration; under his guidance, clinicial research went forward with good teaching, so that his department soon achieved national importance both in education and in investigation.

He felt strongly the obligations of a physician as a public servant. He was a major in the Medical Corps, on active duty in France during the First World War, and he was a member of the Louisiana State Board of Health, acting as its president from 1940 to 1942.

He enjoyed writing and before he left Philadelphia was fortunate enough to acquire editorial experience through his position as assistant editor and editor of the *American Journal of Medical Sciences.* When he came to his new post, he at once took an interest in the *New Orleans Medical and Surgical Journal,* presently assuming the task of developing it and contributing to it both through original articles and through editorials. His major literary achievement, however, was the editing of his "Textbook on Internal Medicine." This appeared in 1932 and became popular immediately; in subsequent editions and reprintings it has continued to be used widely both by medical students and by practitioners.

Dr. Musser's way of life was founded on two simple but enduring ideals: an unselfish desire to serve his fellows and a sincere enthusiasm for acquiring new knowledge in clinical medicine. Add to these imagina-



JOHN H. MUSSER, M.D.
1883-1947

tion, humor, gentleness of manner, tact, unmistakable honesty and integrity, and it is easy to understand why he made friends wherever he went. Physicians over the entire country grew to look on him as a

leading influence in American medicine and showed him this as best they could. They elected him president of the American College of Physicians in 1929, vice president of the American Medical Association in 1933, member of its Council on Medical Education and Hospitals in 1934, its first representative on the American Board of Internal Medicine when the Board was incorporated in 1936 and Honorary Master of the American College of Physicians in 1947, and they made him a member of such organizations as the American Society of Clinical Investigation, the Association of American Physicians, the American Clinical Climatological Association and certain smaller and more intimate interurban clinical or research clubs.

The ARCHIVES was fortunate in having Dr. Musser join its editorial board in 1932. His wisdom, his many medical contacts, his unselfishness, his enthusiasm and his honesty were as perceptible here as they were in his other fields of interest. He strove to improve the quality of the periodical so that it might continue to be of ever increasing usefulness. His influence will be lasting.

Book Reviews

Practical Physiological Chemistry. By Philip B. Hawk, Bernard L. Oser and William H. Summerson. Twelfth edition. Price, $10. Pp. 1323. Philadelphia: The Blakiston Company, 1946.

When a book grows to be forty years old, one of the problems it faces is how to avoid passage into a condition once described by President Theodore Roosevelt as the state of innocuous desuetude. Dr. Hawk's textbook appears to have found the answer in an entirely satisfactory manner.

In 1907, when Dr. Hawk was demonstrator of physiologic chemistry in the department of medicine at the University of Pennsylvania, he made time to write the first edition. This was before the days of the ARCHIVES, but *The Journal of the American Medical Association* reviewed the book at once. The review described it as something more than an ordinary laboratory manual and something less than a thorough treatise on physiologic chemistry. Besides giving helpful directions for mapping a systematic course in this complicated subject, it described technics and gave an intelligent discussion of recent advances in the entire field of biochemistry. It promised to be valuable not only to undergraduate students but also to clinicians and investigators.

The growth of knowledge in physiologic chemistry since then has been enormous, so that the present edition, by necessity, is three times as large as was its parent. Yet the character of the book is unchanged; in modern dress it discusses recent invasions of the field of physiology by chemistry and physics, it describes with great clarity and specificity physical and chemical laboratory methods now in use and it continues to deserve the same warm welcome which it has always received. The twelfth edition of Hawk's "Practical Physiological Chemistry" will lead a useful and popular life until the thirteenth is forthcoming.

Functional Cardiovascular Disease. By Meyer Friedman, M.D., Lt. Col., Med. Res. Corps, U. S. A.; Director, Harold Brunn Institute for Cardiovascular Research, Mt. Zion Hospital; Instructor in Medicine, Stanford Medical School, San Francisco; formerly Consultant in Medicine and Cardiologist, Tripler General Hospital, Honolulu. Cloth. Price, $3. Pp. 266. Baltimore: Williams & Wilkins Company, 1947.

From the title one might think that this book dealt with cardiac arrhythmias, so-called functional murmurs and related topics, but this is not true. It is a full and complete exposition of the disorder known as neurocirculatory asthenia, effort syndrome, the soldier's heart and autonomic imbalance and to which perhaps are applied one or two other designations.

The author has gone thoroughly into the subject and has devoted considerable space to the different symptoms. He discusses the precordial pain, the fatigue, the breathlessness and the extracardiac pain, and he offers his explanation for these phenomena. After this he discusses the probable cause, the diagnosis and the treatment of this condition.

When one considers the tremendous amount of work that has already been done on this subject, one realizes that the author has not contributed much new material, but it is equally evident that he has not missed much of the old.

Patients with this condition at all times present a perplexing problem. During a war period the problem is greatly augmented. In the last war these patients were placed, to a large extent, in the care of neuropsychiatrists. Whether or not they actually belong with them is still a moot question. It is interesting to see how the author manages to stay on both sides of the fence in this question. He states frankly that he believes that all these cases have a psychiatric element. Then he seems to show in his discussion that every one has a certain nervous instability and that the victim of this disorder is merely more unstable than his fellow who shows no symptoms. Stating it in another way, it might be said that we are all a bit psychoneurotic, some of us more so than others.

The book is a carefully documented work on the subject and merits the attention of every student of cardiovascular disease.

Tuberculosis as It Comes and Goes. By Edward W. Hayes, M.D. Second edition. Price, $3.75. Pp. 220, with 43 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1947.

The preface of this small volume states that the book is intended for patients, but much of the material would seem to be over the heads of all but highly intellectual patients, and some material is too controversial for anyone but the specialist. Slight inaccuracies also exist with regard to the bacteriology of the disease. In addition, there is a tendency to go out of the way at times to mention certain controversial theories or discussions, as Ornstein's, Dock's and Hruby's, without mentioning other equally or more plausible theories.

There are gems for patients, however, that have been garnered from the experience of an unquestionable master of the art of treating tuberculosis. No better advice for the intellectual patient at least has ever been written. The book goes into details that only experienced physicians (and ex-patients) could know.

In addition to explanations of most phases of the disease, there are a hundred and one correct details of sanatorium life. With the assistance of Dr. de Rycke, the author has elaborated on the selection of proper mental relaxation, the supreme importance of the attitude of the mind, the role of the physician in the mental as well as physical control and what the patients' visitors should and should not do.

The illustrations are well constructed diagrams made from roentgenograms on the author's own patients and show the extent of the disease and a great variety of its complications.

The printing is done in the usual excellent manner of the publishers, the type is large and pleasing to read and the style is sufficiently smooth to make interesting "browsing" for patients and for many workers in the field of tuberculosis. The book is also to be recommended for general practitioners and even specialists who are desirous of learning more of the fine points in the treatment of this disease.

Microbial Antagonisms and Antibiotic Substances. By Selman A. Waksman. Revised edition. Price, $4. Pp. 415. New York: The Commonwealth Fund, 1947.

Things move quickly in the domain of antibiotics, and the book of today is easily obsolete tomorrow. One welcomes, therefore, a new edition of so important a treatise as Dr. Waksman's. In this revision the number of pages has grown to 415 from 350 in the old edition; the number of references is now 1,053 instead of 1,016. Nowhere is progress more evident than in the chapter on the "chemical nature of antibiotic substances," in which appear many precise formulas not yet worked out at the time of the first edition. The Commonwealth Fund has done a

real service to medicine in producing a scholarly and authoritative compendium of knowledge in such an important field.

Pulmonary Tuberculosis. By R. Y. Keers, M.D., and B. G. Rigden, M.D. Second edition. Price, $5. Pp. 277. Baltimore: Williams & Wilkins Company, 1947.

An ideal textbook on any subject is a difficult achievement, but the work by Dr. Keers and Dr. Rigden approaches that goal as closely as is possible in the space allowed. The authors' aims have been to restrict the size to suit the convenience of those for whom the book is intended i. e., "students and practitioners" —busy people who have no time for controversial matters or inconsequential minutiae.

On the whole, the work shows that the authors are on familiar ground throughout and have in every important discussion given the correct and most widely accepted method. The subject is discussed in the usually accepted order of sequence: bacteriology, pathology, epidemiology and resistance, diagnosis, differential diagnosis, prognosis and treatment. The latter includes, in addition to the usual methods, after-care, rehabilitation and the treatment of tuberculosis as a national problem.

It would be too much, however, to expect the book to be entirely above reproach. The dismissal of all mycoses with a short paragraph on actinomycosis may be fair enough for England, but it will not suffice for other sections of the earth, even in a limited textbook. Blastomycosis and coccidioidal infections should be mentioned, if moniliasis and histoplasmosis are not. Tularemia and brucellosis might well be considered, as well as mediastinal Hodgkin's disease, lymphosarcomas and cysts of various types. The Gaffky scale is generally thought to have outlived its usefulness, and "antiformin" (sodium hydrochlorite solution) has been abandoned long ago in sputum culturing. The new science of bronchospirometry could well have been included without adding too much to the volume of the book. The illustrations of pathologic processes are only fair, but the roentgenograms are abundant, well chosen, of good quality and well reproduced. Besides, each of the "skiagrams" has a fine companion chart to explain the abnormalities. There is no bibliography except for a few references in relation to the chapter on epidemiology and resistance.

The printing is well done, the type easy to read and the binding of the best. The book is truly all it claims to be and more.

Differential Diagnosis of Jaundice. (General Practice Manuals.) By L. Schiff, Ph.D., M.D. Price, $5.50. Pp. 313, with 38 illustrations. Chicago: Year Book Publishers, Inc., 1946.

This little book gives an account of diseases of the liver. It is well written, sound and up-to-date and includes many references to the current periodical literature. It makes pleasant and useful reading for the physician interested in this phase of medicine.

Medical Clinics of North America. Chicago Number: Symposium on Advances in Clinical Medicine. Pp. 258, with 41 illustrations. Philadelphia: W. B. Saunders Company, 1947.

This Chicago number of the Medical Clinics of North America contains some unusually useful reviews of several current medical problems. Among these are

the electrocardiographic studies of Katz and Weinstein, discussions of steatorrhea by Ricketts and his associates, a description by Dakin of the psychosomatic approach in general practice and a satisfactory review of information on the Rh factor by Potter. The volume contains numerous other excellent articles and is developed in a manner that should make it of great usefulness to the physician in general practice.

C-Vitaminstudier: Om korrelationerne mellem blodserumascorbinsyreindholdet, den gennem kosten indgivne C-vitaminmaengde og visse saakaldte D-hypovitaminotiske symptomer, specielt gingivitis. By Marcus Ottsen. Pp. 305. Copenhagen: Thaning and Appels Forlag, 1942.

This monograph presents studies in which a correlation is sought between the vitamin C content of the diet, the serum ascorbic acid level and the clinical conditions which might have their origin in a deficient intake of vitamin C. The subjects were 70 nurses from a municipal hospital in Copenhagen who recorded their own diets and 87 children, aged 9 to 14 years, from an asylum for feebleminded children. Of the children, 10 were on a carefully weighed dietary, while 77 received a diet in which each meal was supervised and the number of portions ingested were recorded. The third group consisted of 249 persons whose intake of vitamin C was known approximately from "data obtained about the diet." Obervations on the nurses extended over three to four weeks and those on the children three weeks.

Serum ascorbic acid content was determined by the method of Lund and Lieck, using methylene blue, and of Farmer and Abt, using 2-6 dichlorophenolindophenol. Foodstuffs when analyzed for ascorbic acid were homogenized with 10 per cent trichloroacetic acid if protein or with 10 per cent acetic acid if fruits or vegetables and centrifuged or filtered, and the clear fluid was titrated with 2-6 dichlorophenolindophenol.

The author found no specific correlation between intake of vitamin C, serum ascorbic acid level and such clinical conditions as gingivitis, bleeding of the gums or osseous changes associated with the teeth. In a group of 79 puerperal women, simple gingivitis was found to be commoner in those with serum ascorbic acid levels ranging from 0 to 0.09 mg. per hundred cubic centimeters than in those with serum ascorbic acid values of 0.10 mg. or higher.

No correlation was found to exist between the intake of vitamin C, serum ascorbic acid level and the hemoglobin content of the blood. Studies showed that there was no correlation between capillary fragility and vitamin depletion.

The latter half of the book is devoted to protocols of patients and analyses of the diets used. The tables in this section represent a great expenditure of time and effort. It apparently is assumed that the three to four week period of the disease is typical for the subject. It appears from the tables that data on some subjects were obtained during the winter and on others during the summer months. It would seem of interest to have data on the same patient collected for both seasons and preferably continuously.

Short summaries in both English and German are included.

Medical Research: A Symposium. Edited by Dr. Austin Smith. Price, $5. Pp. 169, with 17 illustrations. Philadelphia: J. B. Lippincott Company, 1946.

This book contains eight essays which deal with medical research and its importance. Each essay is well written and is apparently designed for nonmedical rather than for professional use. This is the kind of a book that hospital or uni-

versity trustees should read, and it should be presented to public-spirited citizens who might wish to learn about modern medicine and its aspirations.

The concluding chapter discusses medical photography. Anyone will find this chapter interesting.

La silicosis pulmonar. By Hugo Dooner, M.D., with a prologue by Prof. R. Armas Cruz. Pp. 195, with 23 illustrations. Santiago de Chile: Empresa Editora Zig-Zag, S. A., 1944.

This small monograph on pulmonary silicosis is an excellent compilation of the facts on a most interesting disease. The information is garnered both from personal experiences and from an extensive review of the literature. However, there are so few physicians in the United States who can read Spanish with any degree of accuracy that it is doubtful if the book will be used by more than the limited few.

Gynäkologische Diagnostik. By Dr. Neuweiler, Professor of Gynecology and Obstetrics, University of Bern, Switzerland. Price, 58 Swiss francs. Pp. 474, with 406 illustrations. Bern, Switzerland: Hans Huber; New York: Grune & Stratton, Inc., 1946.

This comprehensive tome, for the use of general practitioners and students, devotes four hundred and seventy-four pages to the diagnosis of genitourinary diseases of women. It is the first contribution to the gynecologic textbook literature in German to come out of Switzerland since World War II. The book is written in plain and concise German. The discussions cover the broad aspects of gynecology adequately, with just enough detail to make reading easy. Print and paper are of good quality and most of the illustrations are clear and representative. The exceptions are reproductions of photomicrographs which lack definition. The arrangement of the chapters is logical, and the substance is refreshingly free from long-winded theoretic discussions. The index is rather limited, but the arrangement of individual subjects within each chapter compensates for this.

Subjects like hysterosalpingography, menstruation and its aberrations, colposcopy and backache have been treated with great thoroughness and are a distinct contribution to the literature on diagnostic procedures. Other diagnostic problems, such as the interpretation of cellular contents of vaginal deposits and endocrine dyscrasias, could have been treated more exhaustively. However, the author points out that his contribution is a *Leitfaden* (a guide) and not meant to replace general textbooks, but rather to help the general practitioner and student in organizing a proper diagnostic approach so that he may make a more logical selection of therapeutic measures. The author has relegated laboratory procedures to second place, emphasizing the ever present need for the development of a reliable clinical diagnostic acumen and leaving highly technical laboratory procedures to reference works. The book offers profitable reading for those adequately conversant with literary German.

Gastroenterology in General Practice. By Louis Pelner, M.D., with the collaboration of Louis A. Held and with contributions from Alexander Lewiston and others. Price, $7.50. Pp. 285, with 174 illustrations. Springfield, Ill.: Charles C Thomas, 1946.

In writing this book the author has accomplished rather satisfactorily the purposes of the book discussed in the preface. The book is concise, clearly written, factual and easy to read, and it contains information of practical value, particularly to the general practitioner. The print is pleasingly clear, with large type for

various headings and subheadings. There are numerous illustrations which are clear and helpful. As stated by the author, this is a handbook for everyday use and not a complete reference book. As such it is subject to the same criticism that can be directed toward any book which tries to cover such a large subject in a relatively brief manner, namely, the necessity of presenting without qualifications an arbitrary, one-sided viewpoint on subjects about which there may be differences of opinion among equally competent gastroenterologists.

In instances of patients with symptoms of acute peptic ulcer, many gastroenterologists would not agree with the author's method of feeding the patient every two hours instead of every hour.

The author is to be commended for the chapters on pharmacology of the drugs affecting the autonomic nerves of the gastrointestinal tract and the psychosomatic aspects of gastrointestinal disease.

The busy practitioner will find this a handy and practical addition to his library.

Le problème des tuberculoses atypiques. By R. Burnand and others. Pp. 436, with 20 illustrations. Paris: Masson & Cie, 1946.

In his introduction, Dr. Burnand defines his subject as follows: "The atypical tuberculoses are all the incomplete or irregular pathological manifestations which, according to certain indications, principally clinical, seem to indicate an infection by the tuberculous virus but which fail to fulfill the usual criteria either anatomical or bacteriological for the diagnosis of tuberculosis." He points out that the modern desire to simplify and standardize the classification of tuberculosis has a tendency to exclude from this diagnosis all diseases or syndromes in which tubercle bacilli cannot be demonstrated in the secretions or excretions of the body. This in turn leads to ignorance of the greater portion of tuberculosis which is clinically submerged or latent.

The French schools of phthisiology and bacteriology have been for many years explorers of the difficult and shadowy fields to which this book is a guide. Here are brought together the results of studies and clinical observation by these workers in chapters written by members of the faculties of Swiss universities, principally the University of Lausanne. Burnand writes on pulmonary pathology, including epituberculosis, Loeffler's syndrome, sarcoidosis, emphysema and tuberculotoxic states. Jaeger covers the cutaneous pathologic processes of tuberculous and paratuberculous lesions of the skin. Amsler and Verrey contribute a chapter on ocular forms of tuberculosis. Tuberculous rheumatism of the type of Poncet is reviewed by Martin. The second section is devoted to the pathologic anatomy of the atypical forms of tuberculosis and is written by Nicod. The third section consists in a review of the bacteriology of non-acid-fast and filterable forms of the tubercle bacillus by Dr. P. Hauduroy.

Dr. Burnand binds the whole together with his introduction and a concluding chapter summing up the evidence for the tuberculous nature of many of these conditions. With charming frankness he says that the authors have been merely "trying to project some light into these obscurities." Much of the work referred to has been done in France, Germany and Switzerland during World War II, and hence there are few references to English or American articles in the bibliographies attached to the various chapters. Typography and paper are excellent in this paper-bound volume printed in Switzerland. Those interested in the classification of tuberculosis or in any of the conditions reviewed by the authors will find in it stimulating reading.

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